EXHIBIT K

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10- Q

✓ **Quarterly Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**
for the quarterly period ended October 2, 2016
or

❑ **Transition Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**
for the transition period from to
Commission file number 1- 3215

(Exact name of registrant as specified in its charter)

NEW JERSEY	22- 1024240
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933
(Address of principal executive offices)
Registrant's telephone number, including area code (732) 524- 0400

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. ✓ Yes ❑ No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S- T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). ✓ Yes ❑ No

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non- accelerated filer, or a smaller reporting company. See definitions of "large accelerated filer", "accelerated filer" and "smaller reporting company" in Rule 12b- 2 of the Exchange Act.

Large accelerated filer ✓	Accelerated filer ❑	Non- accelerated filer ❑ (Do not check if a smaller reporting company)	Smaller reporting company ❑

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b- 2 of the Exchange Act). ❑ Yes ✓ No

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date.
On October 28, 2016, 2,720,531,728 shares of Common Stock, $1.00 par value, were outstanding.

JOHNSON & JOHNSON AND SUBSIDIARIES

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Canadian Proceedings

In March 2013, Hospira filed an impeachment proceeding against The Kennedy Institute of Rheumatology (Kennedy) challenging the validity of a Canadian patent related to REMICADE® (a Feldman patent), which is exclusively licensed to JBI. In October 2013, Kennedy, along with JBI, Janssen Inc. (Janssen) and Cilag GmbH International (both affiliates of JBI), filed a counterclaim for infringement against Celltrion and Hospira. The counterclaim alleges that the products described in Celltrion's and Hospira's marketing applications to Health Canada for their subsequent entry biologics (SEB) to REMICADE® would infringe the Feldman patents owned by Kennedy. A trial in the patent action concluded in October 2016, and closing arguments are scheduled for January 2017.

In January 2014, Health Canada approved Celltrion's SEB to REMICADE®, allowing Celltrion to market its infliximab biosimilar in Canada, regardless of the pending patent action. In June 2014, Health Canada approved Hospira's SEB to REMICADE®. In July 2014, Janssen filed a lawsuit to compel the Canadian Minister of Health to withdraw the Notice of Compliance for Hospira's SEB because Hospira did not serve a Notice of Allegation on Janssen to address the patent listed by Janssen on the Patent Register. In March 2015, the parties entered into a settlement agreement whereby Health Canada agreed to a Consent Judgment setting aside Hospira's Notice of Compliance, subject to Health Canada's appeal, which was filed in June 2015. Nevertheless, Hospira began marketing an infliximab biosimilar as a distributor under Celltrion's Notice of Compliance. In October 2016, the appeals court reversed the Consent Judgment. Hospira continues to market and sell its infliximab biosimilar in Canada.

In Canada, if any of the REMICADE® related patents discussed above is found to be invalid following all appeals, such patent could not be relied upon to prevent the further introduction of infliximab biosimilars.

Litigation Against Filers of Abbreviated New Drug Applications (ANDAs)

The following summarizes lawsuits pending against generic companies that have filed Abbreviated New Drug Applications (ANDAs) with the FDA, or undertaken similar regulatory processes outside of the United States, seeking to market generic forms of products sold by various subsidiaries of Johnson & Johnson prior to expiration of the applicable patents covering those products. These ANDAs typically include allegations of non-infringement, invalidity and unenforceability of the applicable patents. In the event the subsidiaries are not successful in these actions, or the statutory 30- month stays of the ANDAs expire before the United States District Court rulings are obtained, the third- party companies involved will have the ability, upon approval of the FDA, to introduce generic versions of the products at issue to the market, resulting in the potential for substantial market share and revenue losses for those products, and which may result in a non- cash impairment charge in any associated intangible asset. In addition, from time to time, subsidiaries may settle these actions and such settlements can involve the introduction of generic versions of the products at issue to the market prior to the expiration of the relevant patents.

CONCERTA®

In December 2014, Janssen Inc. and ALZA Corporation filed a Notice of Application against Actavis Pharma Company (Actavis) in response to Actavis' Notice of Allegation seeking approval to market a generic version of CONCERTA® before the expiration of Canadian Patent No. 2,264,852 (the '852 patent). The hearing was held in September 2016 and the parties are awaiting a decision. Janssen and ALZA are seeking an order enjoining Actavis from marketing its generic version of CONCERTA® before the expiration of the '852 patent.

In October 2016, ALZA Corporation and Janssen Pharmaceuticals, Inc. filed a patent infringement lawsuit in the United States District Court for the District of Delaware against Amneal Pharmaceuticals of New York, LLC and Amneal Pharmaceuticals LLC in response to Amneal's ANDA seeking approval to market a generic version of CONCERTA® before the expiration of United States Patent Nos. 8,163,798 and 9,144,549.

ZYTIGA®

In June and July 2015, Janssen Biotech, Inc. (JBI) received notices of paragraph IV certification from several companies advising of their respective ANDAs seeking approval for a generic version of ZYTIGA® before the expiration of one or more patents relating to ZYTIGA®. In July 2015, JBI, Janssen Oncology, Inc. (Janssen Oncology) and Janssen Research & Development, LLC (collectively, Janssen) and BTG International Ltd. (BTG) filed a patent infringement lawsuit in the United States District Court for the District of New Jersey against several generic ANDA applicants (and certain of their affiliates and/or suppliers) in response to their respective ANDAs seeking approval to market a generic version of ZYTIGA® before the expiration of United States Patent Nos. 5,604,213 (the '213 patent) and/or 8,822,438 (the '438 patent). The generic companies

include Actavis Laboratories, FL, Inc. (Actavis); Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (collectively, Amneal); Apotex Inc. and Apotex Corp. (collectively, Apotex); Citron Pharma LLC (Citron); Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively, Dr. Reddy's); Mylan Pharmaceuticals Inc. and Mylan Inc. (collectively, Mylan); Par Pharmaceuticals, Inc. and Par Pharmaceutical Companies, Inc. (collectively, Par); Sun Pharmaceutical Industries Ltd. and Sun Pharmaceuticals Industries, Inc. (collectively, Sun); Teva Pharmaceuticals USA, Inc. (Teva); Wockhardt Bio A.G.; Wockhardt USA LLC and Wockhardt Ltd. (collectively, Wockhardt); West- Ward Pharmaceutical Corp. (West- Ward); and Hikma Pharmaceuticals, LLC (Hikma). The Court entered a stay of the lawsuit against Par and Citron, as each agreed to be bound by the decision against the other defendants in the action. In February 2016, the Court set a trial date of October 2017. In August 2016, Janssen and BTG dismissed the '213 patent claim against Actavis, the only challenger to the '213 patent, based on Actavis' agreement not to challenge the patent, which expires in December 2016.

In August 2015, Janssen and BTG filed an additional jurisdictional protective lawsuit against the Mylan defendants in the United States District Court for the Northern District of West Virginia, which has been stayed.

In August 2015, Janssen received a notice of paragraph IV certification from Hetero USA Inc., the U.S. Regulatory Agent for Hetero Labs Limited Unit- V, a division of Hetero Labs Limited (collectively, Hetero) advising of Hetero's ANDA seeking approval for a generic version of ZYTIGA® before expiration of the '438 patent. In September 2015, Janssen and BTG filed an amended complaint in the New Jersey lawsuit to allege infringement of the '438 patent by Hetero.

In March 2016, Janssen filed a motion to correct inventorship of the '438 patent to add an inventor and requested that, should the Court order the requested correction, it grant Janssen leave to amend the complaint to recognize BTG as a co- owner of the '438 patent and a co- plaintiff with Janssen with regard to the '438 patent infringement claims.

In March 2016, Janssen received a notice from Amerigen Pharmaceuticals Limited (Amerigen) advising of Amerigen's ANDA seeking approval for a generic version of ZYTIGA® before expiration of the '438 patent. In response, Janssen and BTG filed a patent infringement lawsuit in the United States District Court for the District of New Jersey against Amerigen in May 2016.

In May 2016, Janssen received a notice of paragraph IV certification from Glenmark Pharmaceuticals Inc., on behalf of Glenmark Pharmaceuticals SA, a wholly owned subsidiary of Glenmark Pharmaceuticals Ltd. (collectively, Glenmark) advising of Glenmark's ANDA seeking approval for a generic version of ZYTIGA® before expiration of the '438 patent. In response, in June 2016, Janssen and BTG filed a patent infringement lawsuit in the United States District Court for the District of New Jersey against Glenmark. The parties have stipulated to a dismissal of Glenmark Pharmaceuticals Ltd.

The filing of the above- referenced lawsuits triggered a stay until October 2018 during which the FDA will not grant final approval of the generics' ANDAs unless there is an earlier District Court decision finding the patents- in- suit invalid or not infringed.

In each of the above lawsuits, Janssen is seeking an order enjoining the defendants from marketing their generic versions of ZYTIGA® before the expiration of the relevant patents.

In December 2015, Amerigen filed a petition for an Inter Partes Review in the USPTO seeking to invalidate the '438 patent. In May 2016, the USPTO granted the Inter Partes Review, and a decision as to the validity of the '438 patent is expected by May 2017. In June 2016, Argentum Pharmaceuticals LLC and Mylan Pharmaceuticals Inc. filed petitions for Inter Partes Review in the USPTO seeking to invalidate the '438 patent and moved to join the Inter Partes Review filed by Amerigen. The USPTO granted Argentum's motion for joinder, but deferred a decision on Mylan's motion. In August 2016, Wockhardt Bio AG filed a petition for Inter Partes Review in the USPTO seeking to invalidate the '438 patent.

COMPLERA®

In August and September 2015, Janssen Pharmaceutica NV and Janssen Sciences Ireland UC (collectively, Janssen) and Gilead Sciences, Inc. and Gilead Sciences Ireland UC (collectively, Gilead) filed patent infringement lawsuits in the United States District Courts for the District of Delaware and the District of West Virginia, respectively, against Mylan, Inc. and Mylan Pharmaceuticals, Inc. (collectively, Mylan) in response to Mylan's ANDA seeking approval to market a generic version of COMPLERA® before the expiration of United States Patent Nos. 8,841,310 (the '310 patent), 7,125,879 (the '879 patent) and 8,101,629 (the '629 patent).

In the West Virginia action, in September 2015, Mylan filed an answer and counterclaims asserting invalidity and non- infringement of the '310 patent, '879 patent, and '629 patent, as well as United States Patent No. 8,080,551 (the '551 patent). In

EXHIBIT L

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10- Q

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for the quarterly period ended July 3, 2016
or

❑ **Transition Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**
for the transition period from to
Commission file number 1- 3215

Johnson & Johnson

(Exact name of registrant as specified in its charter)

NEW JERSEY	22- 1024240
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

One Johnson & Johnson Plaza
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Registrant's telephone number, including area code (732) 524- 0400

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Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date.
On July 29, 2016, 2,735,876,843 shares of Common Stock, $1.00 par value, were outstanding.

JOHNSON & JOHNSON AND SUBSIDIARIES

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PREZISTA®

In November 2010, Tibotec, Inc. (predecessor- in- interest to Janssen Products, LP) and Tibotec Pharmaceuticals (predecessor- in- interest to Janssen Sciences Ireland UC) (individually or collectively, with one or more affiliates and successors- in- interest, Janssen) filed a series of patent infringement lawsuits, relating to several patents owned by Janssen or licensed to Janssen from G.D. Searle, against Lupin, Ltd. and Lupin Pharmaceuticals, Inc. (together, Lupin) in the United States District Court for the District of New Jersey in response to Lupin's ANDA seeking approval to market a generic version of Tibotec's PREZISTA® product in various dosage strengths before the expiration of patents relating to PREZISTA®. In June 2013, Lupin, agreed not to seek FDA approval of its ANDA until the November 2017 expiration of the G.D. Searle patents. After a trial regarding the remaining patents, the Court issued a decision in August 2014, holding that the asserted patents are valid and would be infringed by Lupin's marketing of its proposed products. Lupin appealed.

In May 2013, Lupin notified Janssen that it filed an ANDA seeking approval to market a new dosage strength of its generic version of PREZISTA®. In response, Janssen filed a patent infringement lawsuit in the United States District Court for the District of New Jersey, alleging that Lupin's new dosage strength would infringe the same patents that Janssen is asserting against Lupin in the original action. In March 2014, Janssen filed a patent infringement lawsuit against Lupin in the United States District Court for the District of New Jersey, alleging infringement of United States Patent No. 8,518,987 (the ‘987 patent). In January 2015, the Court stayed these cases pending Lupin's appeal of the Court's August 2014 decision in the first action. In April 2015, Lupin filed a petition for Inter Partes review in the United States Patent and Trademark Office (USPTO) seeking to invalidate the ‘987 patent, which was denied in October 2015. In January 2016, Lupin amended its ANDA to reflect a new formulation of darunavir that Lupin alleges does not infringe the relevant Janssen patents. In February 2016, Janssen filed a lawsuit in the United States District Court for the District of New Jersey asserting that Lupin’s new formulation of darunavir infringes the relevant Janssen patents.

In the above lawsuits, Janssen sought orders enjoining Lupin from marketing its generic versions of PREZISTA® before the expiration of the relevant patents. In May 2016, Janssen and Lupin entered into a confidential settlement agreement, pursuant to which the above lawsuits have been dismissed.

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In December 2014, Janssen Inc. and ALZA Corporation filed a Notice of Application against Actavis Pharma Company (Actavis) in response to Actavis’ Notice of Allegation seeking approval to market a generic version of CONCERTA® before the expiration of Canadian Patent No. 2,264,852 (the ‘852 patent). The hearing is scheduled for September 2016. Janssen and ALZA are seeking an order enjoining Actavis from marketing its generic version of CONCERTA® before the expiration of the ‘852 patent.

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In the West Virginia action, in September 2015, Mylan filed an answer and counterclaims asserting invalidity and non- infringement of the '310 patent, '879 patent, and '629 patent, as well as United States Patent No. 8,080,551 (the '551 patent). In March 2016, the District of West Virginia Court stayed the lawsuit and scheduled a conditional trial date in February 2018, in accordance with the schedule in the first- filed Delaware lawsuit described below.

In the Delaware action, in January and March 2016, Janssen and Gilead amended their complaint to add claims for patent infringement with respect to the '551 patent and United States Patent Nos. 7,399,856 (the '856 patent), 7,563,922 (the '922 patent), 8,101,752 (the '752 patent) and 8,618,291 (the '291 patent). In February 2016, Mylan moved to dismiss the suit for lack of personal jurisdiction and, in April 2016, Mylan filed a motion to dismiss, strike or sever the infringement claims regarding the '752 and '291 patents. A trial in the Delaware action has been scheduled for February 2018.

In each of these lawsuits, Janssen is seeking an order enjoining the defendants from marketing their generic versions of COMPLERA® before the expiration of the relevant patents.

XARELTO®

A number of generic companies have filed ANDAs seeking approval to market generic versions of XARELTO®. In October 2015, Janssen Pharmaceuticals, Inc. (JPI) and Bayer Pharma AG and Bayer Intellectual Property GmbH (collectively, Bayer) filed patent infringement lawsuits in the United States District Court for the District of Delaware against Aurobindo Pharma

EXHIBIT M

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approval for a generic version of ZYTIGA® before expiration of the '438 patent. In September 2015, Janssen and BTG filed an amended complaint in the New Jersey lawsuit to allege infringement of the '438 patent by Hetero.

In March 2016, Janssen filed a motion to correct inventorship of the ‘438 patent to add an inventor and requested that, should the Court order the requested correction, it grant Janssen leave to amend the complaint to recognize BTG as a co- owner of the ‘438 patent and a co- plaintiff with Janssen with regard to the ‘438 patent infringement claims.

In December 2015, Amerigen Pharmaceuticals Limited (Amerigen) filed a petition for an Inter Partes Review in the USPTO seeking to invalidate the '438 patent. In March 2016, Janssen Oncology filed its response. Janssen expects the USPTO to issue a decision as to whether to grant the petition by June 2016. In the event that the petition is granted, Janssen expects a decision on the validity of the patent by June 2017. Janssen received a notice from Amerigen advising of Amerigen’s ANDA seeking approval for a generic version of ZYTIGA® before expiration of the ‘438 patent. In response, Janssen and BTG filed a separate patent infringement lawsuit in the United States District Court for the District of New Jersey against Amerigen in May 2016.

The filing of the above- referenced lawsuits triggered a stay until October 2018 during which the FDA will not grant final approval of the generics' ANDAs unless there is an earlier district court decision finding the patents- in- suit invalid or not infringed.

In each of the above lawsuits, Janssen is seeking an Order enjoining the defendants from marketing their generic versions of ZYTIGA® before the expiration of the relevant patents.

COMPLERA®

In August and September 2015, Janssen Pharmaceutica NV and Janssen Sciences Ireland UC (collectively, Janssen) and Gilead Sciences, Inc. and Gilead Sciences Ireland UC (collectively, Gilead) filed patent infringement lawsuits in the United States District Courts for the District of Delaware and the District of West Virginia against Mylan, Inc. and Mylan Pharmaceuticals, Inc. (collectively, Mylan) in response to Mylan’s ANDA seeking approval to market a generic version of COMPLERA® before the expiration of United States Patent Nos. 8,841,310; 7,125,879; and 8,101,629. In September 2015, Mylan filed an answer in the West Virginia action, counterclaiming invalidity and non- infringement of the patents- in- suit as well as United States Patent No. 8,080,551 (the ‘551 patent), and filed a motion to dismiss the Delaware lawsuit for lack of personal jurisdiction. In January 2016, Janssen and Gilead amended their complaint in the Delaware action, adding claims for patent infringement with respect to United States Patent Nos. 7,399,856 and 7,563,922. The District Court in the Delaware Action denied Mylan’s motion to dismiss and set a trial date of February 2018. The District Court in the West Virginia Action has set a trial date of December 2017. In February 2016, Mylan renewed its motion to dismiss the Delaware suit for lack of jurisdiction, and Janssen and Gilead have filed an answer with counterclaims for patent infringement with respect to the ‘551 patent and United States Patent Nos. 8,101,752 and 8,618,291.

In each of these lawsuits, Janssen is seeking an Order enjoining the defendants from marketing their generic versions of COMPLERA® before the expiration of the relevant patents.

XARELTO®

A number of generic companies have filed ANDAs seeking approval to market generic versions of XARELTO®. In October 2015, Janssen Pharmaceuticals, Inc. (JPI) and Bayer Pharma AG and Bayer Intellectual Property GmbH (collectively, Bayer) filed patent infringement lawsuits in the United States District Court for the District of Delaware against Aurobindo Pharma Limited, Aurobindo Pharma USA, Inc., Breckenridge Pharmaceutical, Inc., Micro Labs USA Inc., Micro Labs Ltd., Mylan Pharmaceuticals Inc., Mylan Inc. (Mylan), Prinston Pharmaceutical, Inc., Sigmapharm Laboratories, LLC, Torrent Pharmaceuticals, Limited and Torrent Pharma Inc., in response to those parties’ respective ANDAs seeking approval to market generic versions of XARELTO® before the expiration of Bayer’s United States Patent Nos. 7,157,456 (the ‘456 patent), 7,585,860 (the ‘860 patent) and 7,592,339 (the ‘339 patent) relating to XARELTO®. JPI is the exclusive licensee of the asserted patents. JPI also is seeking an Order enjoining the defendants from marketing their generic versions of XARELTO® before the expiration of the relevant patents.

In November 2015, Mylan moved to dismiss the action. In December 2015, JPI, Bayer, and Mylan stipulated and agreed to dismiss the claims against Mylan, and suspend further briefing and argument on Mylan's motion to dismiss, pending appeals relating to personal jurisdiction over Mylan Pharmaceuticals Inc. in the District of Delaware. In February 2016, a similar patent infringement action by JPI and Bayer against Invagen Pharmaceuticals Inc. (Invagen), in response to Invagen’s notice of paragraph IV certification advising of its ANDA seeking FDA approval for a generic XARELTO® product before expiration of the relevant patents, was consolidated with the original case. The District Court has set a trial date of March 2018.

EXHIBIT N

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10- K

ANNUAL REPORT PURSUANT TO SECTION 13 OF
THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended January 3, 2016 **Commission file number 1- 3215**

JOHNSON & JOHNSON

(Exact name of registrant as specified in its charter)

New Jersey	**22- 1024240**
(State of incorporation)	(I.R.S. Employer Identification No.)
One Johnson & Johnson Plaza **New Brunswick, New Jersey**	**08933**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(732) 524- 0400**

SECURITIES REGISTERED PURSUANT TO SECTION 12(b) OF THE ACT

Title of each class	**Name of each exchange on which registered**
Common Stock, Par Value $1.00	New York Stock Exchange
4.75% Notes Due November 2019	New York Stock Exchange
5.50% Notes Due November 2024	New York Stock Exchange

Indicate by check mark if the registrant is a well- known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ✓ No ❑
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes ❑ No ✓
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Exchange Act during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ✓ No ❑
Indicate by check mark whether the registrant has submitted electronically and posted on its corporate website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S- T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ✓ No ❑
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S- K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10- K or any amendment to this Form 10- K. ✓
Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non- accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b- 2 of the Exchange Act.

Large accelerated filer ✓ Accelerated filer ❑ Non- accelerated filer ❑ Smaller reporting company ❑
(Do not check if a smaller reporting company)

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b- 2 of the Exchange Act). Yes ❑ No ✓
The aggregate market value of the Common Stock held by non- affiliates computed by reference to the price at which the Common Stock was last sold as of the last business day of the registrant's most recently completed second fiscal quarter was approximately $276 billion.
On February 19, 2016, there were 2,759,359,192 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Parts I and III: Portions of registrant's proxy statement for its 2016 annual meeting of shareholders filed within 120 days after the close of the registrant's fiscal year (the "Proxy Statement"), are incorporated by reference to this report on Form 10- K (this "Report").

ZYTIGA®

In June and July 2015, Janssen Biotech, Inc. (JBI) received notices of paragraph IV certification from several companies advising of their respective ANDAs seeking approval for a generic version of ZYTIGA® before the expiration of one or more patents relating to ZYTIGA®. In July 2015, JBI, Janssen Oncology, Inc. and Janssen Research & Development, LLC (collectively, Janssen) and BTG International Ltd. (BTG) filed a patent infringement lawsuit in the United States District Court for the District of New Jersey against several generic ANDA applicants (and certain of their affiliates and/or suppliers) in response to their respective ANDAs seeking approval to market a generic version of ZYTIGA® before the expiration of United States Patent Nos. 5,604,213 (the '213 patent) (expiring December 2016) and/or 8,822,438 (the '438 patent) (expiring August 2027). The generic companies include Actavis Laboratories, FL, Inc. (Actavis); Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (collectively, Amneal); Apotex Inc. and Apotex Corp. (collectively, Apotex); Citron Pharma LLC (Citron); Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively, Dr. Reddy's); Mylan Pharmaceuticals Inc. and Mylan Inc. (collectively, Mylan); Par Pharmaceuticals, Inc. and Par Pharmaceutical Companies, Inc. (collectively, Par); Sun Pharmaceutical Industries Ltd. and Sun Pharmaceuticals Industries, Inc. (collectively, Sun); Teva Pharmaceuticals USA, Inc. (Teva); Wockhardt Bio A.G.; Wockhardt USA LLC and Wockhardt Ltd. (collectively, Wockhardt); West- Ward Pharmaceutical Corp. (West- Ward); and Hikma Pharmaceuticals, LLC (Hikma). The Court entered a stay of the New Jersey lawsuit against each of Par and Citron, as each agreed to be bound by the decision against the other defendants in the New Jersey action. In February 2016, the New Jersey Court set a trial date of October 2017.

In August 2015, Janssen and BTG filed an additional jurisdictional protective lawsuit against the Mylan defendants in the United States District Court for the Northern District of West Virginia. In October 2015, Mylan filed a motion to dismiss the New Jersey lawsuit for lack of personal jurisdiction and improper venue. In February 2016, the West Virginia Court stayed the West Virginia case pending a decision on Mylan's motion to dismiss in the New Jersey lawsuit, but set a conditional trial date of February 2018. The Court will dismiss the West Virginia lawsuit if Mylan's motion to dismiss in New Jersey is denied.

In August 2015, JBI received a notice of paragraph IV certification from Hetero USA Inc., the U.S. Regulatory Agent for Hetero Labs Limited Unit-V, a division of Hetero Labs Limited (collectively, Hetero) advising of Hetero's ANDA seeking approval for a generic version of ZYTIGA® before expiration of the '438 patent. In September 2015, Janssen and BTG filed an amended complaint in the New Jersey lawsuit to allege infringement of the '438 patent by Hetero.

The filing of the above- referenced lawsuits triggered a stay until October 2018 during which the FDA will not grant final approval of the generics' ANDAs unless there is an earlier district court decision finding the patents- in- suit invalid or not infringed.

In December 2015, Amerigen Pharmaceuticals Limited filed a petition for an Inter Partes Review in the USPTO seeking to invalidate the '438 patent.

In each of the above lawsuits, Janssen is seeking an Order enjoining the defendants from marketing their generic versions of ZYTIGA® before the expiration of the relevant patents.

COMPLERA®

In August and September 2015, Janssen Pharmaceutica NV and Janssen Sciences Ireland UC (collectively, Janssen) and Gilead Sciences, Inc. and Gilead Sciences Ireland UC (collectively, Gilead) filed patent infringement lawsuits in the United States District Court for the District of Delaware and West Virginia against Mylan, Inc. and Mylan Pharmaceuticals, Inc. (collectively, Mylan) in response to their ANDA seeking approval to market a generic version of COMPLERA® before the expiration of United States Patent Nos. 8,841,310; 7,125,879; and 8,101,629. In September 2015, Mylan filed an Answer in the West Virginia action that included counterclaims seeking declarations of invalidity and non- infringement of the patents- in- suit as well as United States Patent No. 8,080,551. In September 2015, Mylan filed a motion to dismiss the Delaware lawsuit for lack of personal jurisdiction. In January 2016, Janssen and Gilead filed a first amended complaint in the New Jersey Action adding claims for patent infringement with respect to United States Patent Nos. 7,399,856 and 7,563,922. In addition, in the New Jersey Action, the Court dismissed Mylan's motion to dismiss and set a trial date of February 2018, and in the West Virginia Action, the Court set a trial date of December 2017. In February 2016, Mylan renewed its motion to dismiss for lack of jurisdiction.

In each of the above lawsuits, Janssen is seeking an Order enjoining the defendants from marketing their generic versions of COMPLERA® before the expiration of the relevant patents.

EXHIBIT O

Cancer Management and Research

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REVIEW

Abiraterone in the treatment of metastatic castration-resistant prostate cancer

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Abstract: Androgen deprivation therapy remains the single most effective treatment for the initial therapy of advanced prostate cancer, but is uniformly marked by progression to castration-resistant prostate cancer (CRPC). Residual tumor androgens and androgen axis activation are now recognized to play a prominent role in mediating CRPC progression. Despite suppression of circulating testosterone to castrate levels, castration does not eliminate androgens from the prostate tumor microenvironment and residual androgen levels are well within the range capable of activating the androgen receptor (AR) and AR-mediated gene expression. Accordingly, therapeutic strategies that more effectively target production of intratumoral androgens are necessary. The introduction of abiraterone, a potent suppressor of cytochrome P450 17 α-hydroxysteroid dehydrogenase-mediated androgen production, has heralded a new era in the hormonal treatment of men with metastatic CRPC. Herein, the androgen and AR-mediated mechanisms that contribute to CRPC progression and establish cytochrome P450 17 α-hydroxysteroid dehydrogenase as a critical therapeutic target are briefly reviewed. The mechanism of action and pharmacokinetics of abiraterone are reviewed and its recently described activity against AR and 3-β-hydroxysteroid dehydrogenase is discussed. The Phase I and II data initially demonstrating the efficacy of abiraterone and Phase III data supporting its approval for patients with metastatic CRPC are reviewed. The safety and tolerability of abiraterone, including the incidence and management of side effects and potential drug interactions, are discussed. The current place of abiraterone in CRPC therapy is reviewed and early evidence regarding cross-resistance of abiraterone with taxane therapy, mechanisms of resistance to abiraterone, and observations of an abiraterone withdrawal response are presented. Future directions in the use of abiraterone, including optimal dosing strategies, the role of abiraterone in earlier disease settings, including castration sensitive, biochemically recurrent, or localized disease, and the rationale for combinatorial treatment strategies of abiraterone with enzalutamide and other targeted agents are also discussed.

Keywords: castration-resistant, abiraterone, CYP17A, androgen, intracrine

Introduction to castration-resistant prostate cancer (CRPC)

The primary treatment modality for patients with metastatic prostate cancer is androgen deprivation therapy (ADT). However, treatment is uniformly marked by progression to CRPC over a period of about 18 months, with an ensuing median survival of 1–2 years. Importantly, it is now clear that "androgen independent" or "hormone refractory" tumors remain sensitive to hormonal activation, and that despite suppression of circulating testosterone (T), residual tumor androgens and androgen axis activation play a prominent role in mediating CRPC progression.[1] Numerous molecular features

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have been shown to contribute to AR signaling in CRPC and demonstrate that ongoing AR activation may occur via both ligand-dependent and ligand-independent mechanisms. As a consequence, the efficiency of AR activation at low or absent ligand levels can be enhanced and AR ligand specificity can be broadened, potentiating the persistent activation of AR signaling in CRPC tumors.

Residual tumor androgens in CRPC

Castration does not eliminate androgens from the prostate tumor microenvironment and residual androgen levels are well within the range capable of activating the AR and AR-mediated gene expression,[2–5] strongly suggesting that intratumoral androgens are clinically relevant in driving castration-resistant tumors. While the efficacy of ADT is based on achieving castrate levels of serum T (defined as <20 ng/dL), measurement of prostatic tissue androgen levels in locally recurrent and metastatic CRPC has consistently demonstrated the presence of residual tumor androgens. In advanced prostate cancer, Mohler et al found that prostatic T levels in castrate patients with locally recurrent tumors were equivalent to those of benign prostatic hyperplasia patients and that intratumoral dihydrotestosterone (DHT) levels were only reduced 80% (to ~0.4 ng/g).[3] In another study, T levels in metastatic tumors obtained via rapid autopsy from men with CRPC were found to be approximately three-fold higher than T levels within primary prostate tumors from untreated (eugonadal) patients (T 0.74 ng/g; DHT 0.25 ng/g).[6]

Data derived from in vitro and in vivo studies have determined that tissue DHT levels of 0.5–1.0 ng/g (the range observed in prostatic tissue of castrated patients) are sufficient to activate the AR, stimulate expression of AR-regulated genes, and promote androgen-mediated tumor growth.[3,7–10] Moreover, residual tissue androgens participate in nearly every mechanism by which AR-mediated signaling leads to the development of castration-resistant disease, including AR overexpression, AR mutations that alter ligand binding, and alterations in AR coregulators, all of which result in hypersensitization of AR to activation by low levels of residual androgens.[11] The maintenance of intratumoral androgens can be accounted for, in part, by intratumoral or intracrine biosynthesis of steroid hormones, either via the uptake and conversion of adrenal androgens (as initially put forward by Labrie et al),[12] or potentially via de novo steroidogenesis.[6,13–18]

AR alterations in CRPC

AR overexpression is a well-recognized feature of CRPC and believed to be a critical driver of CRPC progression.[3,17,19–27] Potential mechanisms responsible for increased AR expression include amplification of the AR locus itself, increased transcription rates, or stabilization of the messenger RNA or protein. AR overexpression not only mediates sensitivity to low ligand concentrations, but has been demonstrated to convert anti-androgens such as bicalutamide and flutamide from antagonists to agonists via changes in composition of coactivators recruited to the AR promoter.[28,29]

Several well-characterized AR mutations can result in promiscuous binding and activation of the AR by weak adrenal androgens and other steroid hormones, including dehydroepiandrosterone (DHEA), progesterone, estrogens, and cortisol.[30–35] Other mutations convert AR antagonists (flutamide and bicalutamide) into potent agonists.[36] Notably, in vitro selection with enzalutamide has revealed a new mutation (F876L) which mediates conversion of enzalutamide to an AR agonist while maintaining sensitivity to bicalutamide.[37,38] This mutation also confers resistance to the second-generation AR antagonist ARN509, and has been detected in circulating tumor DNA from ARN509-treated patients.[39] While the frequency of AR mutation in CRPC tumors treated with luteinizing hormone (LH)-releasing hormone agonist and first-generation AR antagonists is low (8%–25%),[33] the frequency of these mutations may become more frequent with the advent of potent antagonists of AR signaling.

Constitutively active truncated AR splice variants have recently been recognized as a potential mechanism of CRPC progression. The expression of certain variants (eg, AR-V7, which can be detected in hormone-naïve prostate cancer) has been associated with a shorter time to disease recurrence following radical prostatectomy.[40,41] High levels of ARV7 and ARV567 were associated with shorter survival in patients with CRPC and bone metastases, consistent with a role in tumor progression.[42,43] Although each variant displays a slightly different structure, they each lack portions of the carboxy-terminal ligand binding domain, resulting in a constitutively active AR.[44]

Clinical evidence of AR axis signaling in CRPC

The clinical importance of ongoing AR pathway activity in CRPC progression is reflected in the rising serum prostate-specific antigen (PSA) levels in patients with CRPC, and is confirmed by clinical responses to treatment strategies that target residual AR axis activity. These include historical responses to adrenalectomy and/or hypophysectomy;[45,46] the limited but consistent ~5% overall survival (OS) benefit seen

in meta-analyses of combined androgen blockade trials;[47–49] the observation that nearly 30% of recurrent prostate tumors demonstrate at least transient clinical responses to secondary or tertiary hormonal manipulation;[50] and most recently, the striking clinical response observed with the novel AR axis inhibitors abiraterone and MDV3100.[51,52]

Mechanism of action and pharmacology of abiraterone

Emerging data suggest residual intratumoral androgens are produced via the uptake and conversion of adrenal androgens, and potentially via de novo synthesis from cholesterol or progesterone precursors within the tumor.[6,13–18] Accordingly, therapeutic strategies that more effectively target production of intratumoral androgens are necessary. Abiraterone is the first to enter clinical practice in a series of novel agents designed to potently target adrenal and tumor androgen production.

Cytochrome P450 17 α-hydroxysteroid dehydrogenase (CYP17A) as a therapeutic target in CRPC

The critical enzyme required for androgen synthesis from cholesterol is CYP17A. Adrenal expression of this enzyme accounts for production of circulating adrenal androgens, including DHEA (which primarily circulates in its sulfated form, DHEA-S) and androstenedione (AED), and a number of studies have demonstrated expression of CYP17A in castration-resistant prostate tumors.[6,53] Given its central role in the production of either adrenal or tumor-derived extragonadal androgen synthesis, CYP17A has emerged as a primary target of novel therapeutics.

CYP17A is a single enzyme that catalyzes the sequential hydroxylase (required for cortisol synthesis) and lyase (required for adrenal androgen synthesis) steps that are required for conversion of C21 pregnenolone and progesterone precursors to the C19 adrenal androgens, DHEA and AED. While ketoconazole (a weak inhibitor of CYP11α-hydroxylase and CYP17A) has been utilized for suppression of residual adrenal androgens in men with CRPC, its limited efficacy and treatment-related side effects prompted the development of more potent CYP17A inhibitors.[54]

Abiraterone acetate is an orally administered, rationally designed small molecule derived from the structure of pregnenolone. It irreversibly inhibits both the hydroxylase and lyase activity of CYP17A with approximately 10–30-fold greater potency than ketoconazole.[55] Because adrenal inhibition of CYP17A results in blockade of glucocorticoid as well as adrenal androgen synthesis, abiraterone is coadministered with prednisone to ameliorate the secondary rise in adrenocorticotropic hormone (ACTH) that can lead to excess mineralocorticoid synthesis (Figure 1, discussed further below).[56]

Unintended activity of abiraterone against other AR pathway targets

Abiraterone was designed as a selective, irreversible inhibitor of CYP17A. However, most likely due to its steroidal structure, abiraterone has been found to inhibit other AR pathway targets including AR itself, as well as 3β-hydroxysteroid dehydrogenase, another key enzyme required for androgen synthesis.

While not as potent as the first-generation nonsteroidal AR inhibitors (eg, bicalutamide), abiraterone demonstrated measurable AR antagonism at 1–10 μmol/L, a clinically achievable concentration.[57] Pharmacokinetic studies (discussed below) have found plasma abiraterone levels to be 1.2–5 μmol/L following a 1,000 mg dose in fasting patients. Galeterone, another novel CYP17A antagonist, has been demonstrated to have anti-AR activity as well, and actually has increased potency compared to abiraterone in this regard.[58] Interestingly, an early study demonstrated that ketoconazole can also inhibit the AR, although not at clinically achievable doses.[59]

With regard to its activity against 3β-hydroxysteroid dehydrogenase type I, abiraterone was shown to inhibit two key reactions mediated by this enzyme. Abiraterone, again at clinically achievable concentrations of 2.1–8.8 μmol/L, inhibited the conversion of DHEA to AED, and of 5α-androstanediol to T, with concomitant suppression of AR-regulated gene expression.[60] These data suggest that even though maximal inhibition of CYP17A is achieved at the currently approved 1,000 mg dose, dose escalation may increase the efficacy of abiraterone by taking advantage of its ability to inhibit multiple AR pathway targets. Clinical trials evaluating this hypothesis are ongoing.

Pharmacokinetics of abiraterone

Abiraterone is administered as the pro-drug abiraterone acetate which has improved oral bioavailability and shows near complete conversion to abiraterone in the blood. In preclinical toxicology studies, abiraterone reduced the weights of androgen dependent organs such as the prostate and had minimal side effects in other organs.[61] First-in-man studies demonstrated the ability of abiraterone to reduce

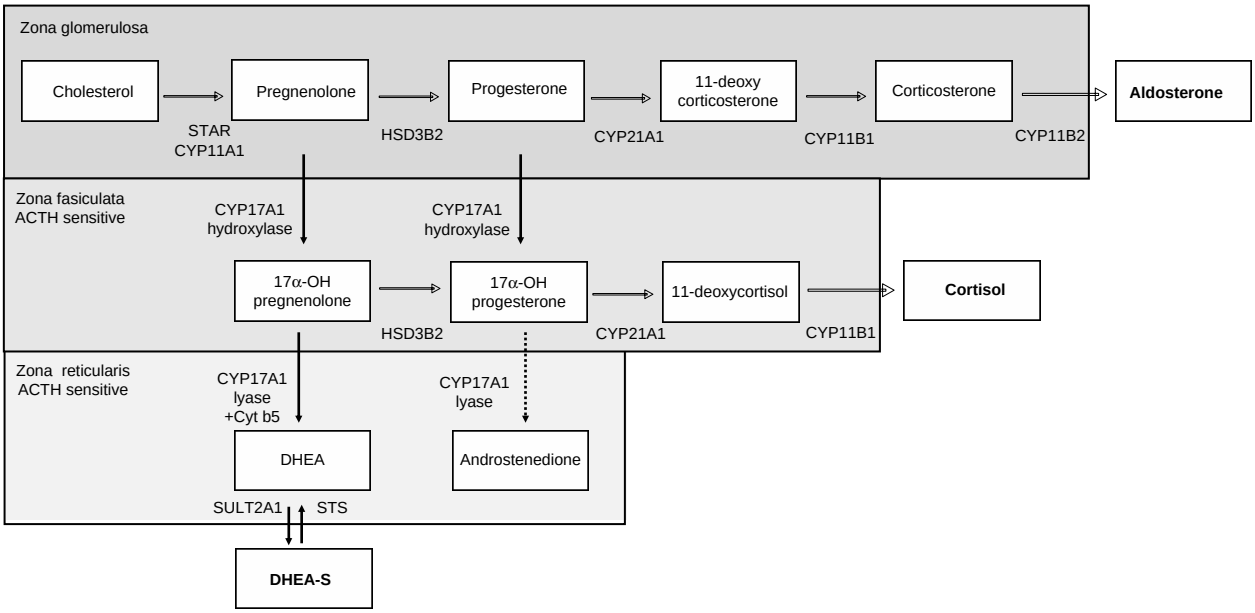

Figure 1 Steroid hormone pathways in zones of the adrenal gland. Steroid synthesis in the adrenal gland occurs in three zones, each with a specific complement of enzymes that determine the steroids produced. The zona glomerulosa contains the enzymes necessary to produce aldosterone. The zona fasciculata and reticularis additionally express CYP17A. The hydroxylase activity of CYP17A is active in the zona fasciculata resulting in the production of cortisol. However, the lyase activity of CYP17A requires the cytochrome b5 coregulator which is only present in the zona reticularis. This drives efficient production of DHEA which is then sulfated to DHEA-S. 17α-OH progesterone is a relatively poor substrate for CYP17A lyase (dotted arrow), and thus androstenedione is formed at lower levels. The zona fasciculata and zona reticularis are sensitive to the ACTH feedback stimulation that occurs when cortisol production is suppressed by inhibition of CYP17A.
Abbreviations: 17α-OH, 17α-hydroxy; ACTH, adrenocorticotropic hormone; CYP11A, cytochrome P450 11α-hydroxylase; CYP11B, cytochrome P450 11β-hydroxylase; CYP17A, 17α-hydroxylase/17,20 lyase/17,20 desmolase; CYP21A, cytochrome P450 21α-hydroxylase; Cyt b5, cytochrome b5; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone-sulfate; HSD3B, 3-β-hydroxysteroid dehydrogenase; STAR, steroidogenic acute regulatory protein.

serum T levels in both castrate and noncastrate men. In castrate men dose escalation to 500 mg was required to achieve the target effect, a 75% decrease in T levels. The duration of suppression following a single dose was variable, ranging from 2–5 days. In noncastrate men, repeat dosing at ≥800 mg daily was required to maintain T suppression, and was accompanied by a marked rise in LH that may have prevented sustained T suppression.[62]

Two Phase I trials in chemotherapy-naïve men with metastatic CRPC were performed to determine the recommended dose for Phase II testing. No dose-limiting toxicities were observed at doses up to 2,000 mg/daily, but 1,000 mg was chosen for expansion as a plateau in pharmacodynamic effect was observed at doses >750 mg. Substantial variability in drug absorption was observed, with up to nine-fold differences in serum pharmacokinetic parameters within the 1,000 mg cohort. Maximal drug concentrations were achieved within 2–4 hours, with a terminal half-life of approximately 12 hours.[63,64]

Impact of food on abiraterone exposure

Notably, drug exposure was five to seven-fold higher when abiraterone was administered with a low-fat meal (7% fat, 300 calories) and over ten-fold higher with a high-fat meal (57% fat, 825 calories) as compared to the fasted state. To minimize the variability in absorption, abiraterone is labeled for administration as 1,000 mg (four 250 mg tablets) daily on an empty stomach, defined as 1 hour before or 2 hours after a meal.[65] Clinical trials evaluating abiraterone in the fed and fasted state are ongoing (NCT01424930),[66] as are trials evaluating lower doses of abiraterone taken with food (NCT01543776).[67] If borne out, these approaches could decrease drug costs, as well as decrease the potential risk of drug interactions (see below) if a patient accidentally takes the agent with food.[65,68]

In a dedicated renal impairment trial, renal dysfunction did not impact pharmacokinetic profiles and no dose adjustment is necessary for renal impairment.[69] Abiraterone is bound to plasma proteins including albumin and is primarily excreted in the feces.[70]

Efficacy studies

Phase I and II data

Phase I and II studies demonstrated that abiraterone suppresses serum androgen levels, and achieves PSA and clinical responses in chemotherapy-naïve and docetaxel-treated CRPC patients. No dose-limiting toxicities were associated with abiraterone, and anti-tumor activity and

PSA responses were observed at all dose levels. While the highest tolerated dose was 2,000 mg/day, all Phase II and III studies have used the 1,000 mg/day dose, as the impact of therapy on steroids upstream of CYP17A plateaued at doses >750 mg/day.[63]

In eugonadal men, abiraterone transiently suppresses T levels by >50% (but a corresponding rise in LH levels overcomes inhibition of gonadal androgen synthesis), while in castrate men, abiraterone further suppresses castrate serum T levels by ≥75%.[62] In general, abiraterone suppresses serum DHEA levels by approximately 75% and DHEA-S, AED, and T to essentially undetectable.[63,64] As observed in studies of ketoconazole, higher baseline levels of DHEA-S, DHEA, and AED were present in patients achieving >50% PSA declines. In contrast to progression on ketoconazole, increases in T, AED, or DHEA levels were not observed on progression with abiraterone.[71,72]

In men with chemotherapy- and ketoconazole-naïve metastatic CRPC, a Phase I/II single-agent study of abiraterone demonstrated durable PSA declines >50% in 67% of patients, with partial radiographic responses in 37.5% and a median time to progression (TTP) of 32 weeks.[72] Based on preclinical data that progesterone precursors upstream of CYP17A can activate certain AR mutations, this study also evaluated the addition of corticosteroids at progression and showed that 33% of patients (10/30) had secondary PSA responses following the addition of dexamethasone 0.5 mg/day.[72] A Phase II study of abiraterone combined with prednisone in this population demonstrated PSA declines >50% in 79% of patients and a median TTP of 65 weeks. This study also found that over 48% (11/23) evaluable patients had a transient bone scan flare at 3 months that subsequently showed with improvement or stability.[73] In a second Phase I single-agent study of pre-chemotherapy patients in which 58% were ketoconazole pretreated, PSA declines >50% were noted in 55% of patients at 12 weeks.[64]

In post-docetaxel-treated CRPC patients, a Phase II single-agent study of abiraterone demonstrated PSA declines >50% in 51% of patients (only 17% had received prior ketoconazole), with partial radiographic responses in 27% and a median TTP of 24 weeks.[74] In a Phase II study of abiraterone combined with prednisone, in which 47% of patients were ketoconazole pretreated, PSA declines >50% were observed in 36% of patients with a median TTP of 24 weeks.[75]

Efficacy in ketoconazole-treated patients

Importantly, while ketoconazole-treated patients were specifically excluded in the subsequent Phase III studies, the Phase I/II studies demonstrated that abiraterone has activity in these patients as well. In the pre-chemotherapy Phase I study in which 58% of men (19 of 33) were ketoconazole pretreated, PSA responses >50% were observed in 64% of ketoconazole-naïve patients and 47% of ketoconazole-pretreated patients.[64] In the post-docetaxel study in which 47% of patients (27 of 58) had received prior ketoconazole, PSA declines >50% occurred in 45% of ketoconazole-naïve patients and 26% of ketoconazole-treated patients with a median TTP of 28 and 14 weeks, respectively.[75] These findings demonstrate that abiraterone maintains a reasonable degree of clinical efficacy in CRPC patients previously treated with docetaxel and/or ketoconazole.

Phase III data

Findings from the Phase I and II studies have been subsequently confirmed in Phase III studies in chemotherapy-naïve (COU-AA-302) and post-docetaxel-treated men (COU-AA-301), resulting in US Food and Drug Administration approval of abiraterone for men with metastatic CRPC either before or after treatment with chemotherapy.

COU-AA-301

In the post-chemotherapy setting, 1,195 men with metastatic CRPC progressing after docetaxel were randomized in a 2:1 ratio to abiraterone/prednisone (n=797) or placebo/prednisone (n=398) with a primary endpoint of OS. The median PSA was ~130 ng/dL, 90% of patients had an Eastern Cooperative Oncology Group performance status (PS) of zero to one, the median age was 70 years, and 28% were ≥75 years. Bone, lymph node, and visceral metastases were present in approximately 90%, 40%, and 10% of patients, respectively, and 30% of patients had received more than one prior chemotherapy regimen. Treatment was continued until clinical or radiographic evidence of progression.

At a median follow-up of 12.8 months, the first interim analysis demonstrated an OS benefit for men receiving abiraterone (14.8 months versus 10.9 months for placebo; hazard ratio [HR] 0.646; $P<0.0001$), representing a 35% reduction in risk of death and prompting the independent data monitoring committee to recommend that the study be unblinded and men on the placebo arm be offered abiraterone.[51] An updated analysis at a median survival of 20.2 months demonstrated a median OS of 15.8 months for abiraterone versus 11.2 months for prednisone (HR 0.74; $P<0.0001$), extending the OS benefit to 4.6 months.

All secondary endpoints were statistically significant in favor of abiraterone, including median time to PSA

progression (8.5 months versus 6.6 months), median radiologic progression-free survival (rPFS; 5.6 months versus 3.6 months), and proportion of patients with >50% PSA response (29.5% versus 5.5%). The impact of abiraterone on OS was observed across all subgroups, including patients who had received one (15.4 versus 11.5 months) or two prior chemotherapy regimens (14.0 versus 10.3 months). Notably, patients with a PS of two had worse outcomes, with a median survival of 7.3 months on abiraterone compared to 15.3 months for those with PS of zero to one receiving abiraterone.[76]

While visceral disease was associated with a poorer prognosis, an exploratory analysis reported in abstract form found the absolute benefit in OS from abiraterone to be similar in those with and without visceral disease (8.3–12.9 months in those with visceral disease and 12.3–17.3 months in those without). Analysis of patients by site of disease showed worse outcomes in those with hepatic versus pulmonary visceral metastases, but still a benefit favoring abiraterone over placebo (median OS 4.0–7.3 months for liver metastases and 7.9–13.9 months for pulmonary disease).[77]

Exploratory analyses of COU-AA-301 evaluating the impact of abiraterone on fatigue, pain control, and skeletal-related events suggest abiraterone has efficacy in all these settings. In patients with clinically significant fatigue at baseline, abiraterone significantly increased the number of patients reporting an improvement in fatigue intensity (58.1% versus 40.3%; P=0.0001) as well as the time to fatigue palliation (median 59 days versus 194 days; P=0.0155).[78] In patients with clinically significant pain at baseline, abiraterone significantly increased the number of patients reporting palliation of pain (45% versus 28.8%; P=0.0005), as well as faster palliation (median time to palliation 5.6 months versus 13.7 months; P=0.0018). Median time to occurrence of first skeletal-related event (defined as pathologic fracture, spinal cord compression, or palliative surgery or radiation to bone) was also significantly longer in abiraterone treated patients (25 months versus 20.3 months; P=0.0001).[79]

COU-AA-302

In the pre-chemotherapy setting, 1,088 men with asymptomatic or minimally symptomatic bone and lymph node (but not visceral) metastatic CRPC were randomized 1:1 to abiraterone/prednisone (n=546) or placebo/prednisone (n=542), with co-primary endpoints of rPFS and OS. The median PSA was ~40 ng/dL, about 30% of men were ≥75 years, and approximately 50% had bone-only metastatic disease.

At a median follow-up of 22.2 months, a statistically significant doubling in rPFS from 8.3 months in the placebo arm to 16.5 months was observed in men receiving abiraterone (HR 0.53; P<0.001), accompanied by a trend for increased OS from 27.3 months in the placebo arm to not reached in the abiraterone group (HR 0.75; P=0.01 which did not meet the prespecified P-value of 0.001), again prompting the independent data monitoring committee to recommend that the study be unblinded and men on the placebo arm be offered abiraterone.[80] An updated analysis of OS at a median survival of 27.1 months again trended toward favoring abiraterone at 30.1 months in the placebo arm versus 35.3 months in the abiraterone arm (HR 0.79; P=0.015).[81]

All secondary endpoints were statistically significant in favor of abiraterone, including median time to opiate use (not reached versus 23.7 months), time to initiation of chemotherapy (25.2 months versus 16.8 months), time to PS decline (12.3 months versus 10.9 months), time to PSA progression (11.1 months versus 5.6 months), and proportion of patients with >50% PSA response (62% versus 24%). The impact of abiraterone on rPFS was observed across all subgroups.[80] This study did not include patients with visceral disease or moderate to severe pain; however, the exploratory analyses of these subpopulations in the post-chemotherapy setting discussed above suggest these patients are likely to benefit as well.

Safety and tolerability

Abiraterone is generally well tolerated, with 13% and 19% of abiraterone-treated patients in COU-AA-301 and COU-AA-302, respectively, discontinuing therapy for adverse effects versus 18% and 23% of placebo-treated patients. The most common adverse events in both groups were fatigue, back pain, nausea, constipation, bone pain, and arthralgia, all in the range of 25%–30%. The incidence of urinary tract infection was statistically higher in abiraterone-treated patients (12% versus 7% in placebo; P=0.02).

Mineralocorticoid and electrolyte effects

Inhibition of CYP17A by abiraterone increases mineralocorticoid precursors upstream of CYP17A and decreases glucocorticoids downstream of CYP17A (Figure 1). The latter results in a concomitant elevation of ACTH, which further drives mineralocorticoid production. Phase I and II trials demonstrated that symptoms of mineralocorticoid excess occur in 50%–80% of patients treated with single-agent abiraterone.[56] Mineralocorticoid-related symptoms in the Phase III studies were markedly attenuated by inclusion of prednisone 5 mg twice daily, and were generally of Grade I or II in magnitude, including fluid retention (~33% versus 22%–24% in placebo),

hypertension (~10% versus 8% in placebo), and hypokalemia (~18% versus 9% in placebo).

Dexamethasone, which lacks mineralocorticoid effects and has a longer duration of action, may theoretically be preferable to prednisone and can be used at a dose of 0.5 mg daily.[82] However, a rare incidence (2/100) of orthostatic hypotension was reported following addition of dexamethasone to single-agent abiraterone, possibly due its lack of mineralocorticoid activity in the setting of a rapid decline in circulating mineralocorticoids.[63,64]

Of note, other CYP17A inhibitors such as orteronel and galeterone demonstrate more selective targeting of the lyase but not hydroxylase activity of CYP17A. These agents may be associated with less inhibition of cortisol synthesis and less ACTH/feedback-driven symptoms of mineralocorticoid excess and are being evaluated for use both with and without corticosteroids.

Careful attention should be paid to hypertension and hypokalemia, which should be corrected before and during therapy with abiraterone. Patients should be monitored for hypertension, hypokalemia, and fluid retention at least once a month. Spironolactone is avoided in patients who develop mineralocorticoid-related side effects due to its mixed AR agonist/antagonist activity. Instead, eplerenone, a second-generation mineralocorticoid receptor antagonist in doses of 50–200 mg/day (in divided doses twice daily) can be used in combination with a salt-restricted diet.[83]

While eplerenone does not bind the wild-type AR, it can activate certain AR mutations; however, further data is needed regarding the incidence and clinical significance of these mutations. Alternatively, potassium-sparing epithelial sodium channel antagonists such as amiloride and triamterene (in combination with hydrochlorothiazide if hypertension is significant) can be used in place of or added to eplerenone if necessary.[82,83] In rare instances, additional anti-hypertensive agents may be necessary in patients already receiving prednisone, eplerenone, and diuretics.

Hepatotoxicity

Grade III or IV hepatic transaminase abnormalities (five times the upper limit of normal [ULN]) occurred in approximately 4% of patients in the Phase III studies, usually within the first 3 months of starting treatment, and more commonly in men whose baseline alanine transaminase or aspartate transaminase were elevated. Serum transaminases should be measured at baseline. Transaminases in patients with normal levels should be checked every 2 weeks for the first 3 months of therapy, and then monthly. No dose adjustment is necessary for mild hepatic impairment. For moderate hepatic impairment (Child–Pugh Class B) abiraterone should be started at 250 mg daily, and transaminases should be checked weekly for the first month, then every 2 weeks for the following 2 months, and then monthly.

If aspartate transaminase or alanine transaminase rise above five times the ULN or bilirubin rises above three times the ULN, abiraterone should be held. It should be discontinued if the patient had moderate hepatic impairment at baseline, but in patients with normal hepatic function at baseline it can be restarted at 750 mg daily when liver function tests decline to less than 2.5 times the ULN and total bilirubin is less than 1.5 times the ULN. If hepatotoxicity recurs, a further dose reduction to 500 mg can be attempted (once levels have fallen below the thresholds given above), but recurrence of hepatotoxicity at the 500 mg dose requires discontinuation of the drug.

Cardiotoxicity

The overall incidence of adverse cardiac effects was not statistically increased by abiraterone in COU-001 (13% versus 11% in placebo), although the frequency of cardiac failure was higher in the abiraterone group (2.1% versus 0.7% in placebo). The most frequently reported cardiac events were Grade I and II tachycardia and Grade III or lower atrial fibrillation. A retrospective study of 51 metastatic CRPC patients with at least one cardiac comorbidity and/or controlled risk factor including hypertension (41%), hyperglycemia (30%), dyslipidemia (18%), cardiac ischemia (12%), stroke (9%), or arrhythmias (6%) reported no cardiac events or variation in left ventricular ejection fraction over 6–12 months of follow-up.[84] However, as patients with left ventricular ejection fraction $<$50% were excluded from the Phase III studies, pretreatment assessment and optimization of cardiac status with electrocardiogram and echocardiography may warrant consideration in elderly patients with reduced cardiac function. A significant effect of abiraterone on the QT/QTc interval in patients with CRPC was not observed.[85]

Potential drug interactions

Abiraterone is a strong inhibitor of several microsomal drug metabolizing enzymes, including CYP1A2 and CYP2D6.[86] Abiraterone increased systemic exposure of dextromethorphan (metabolized by CYP2D6) approximately two to three-fold, while the pharmacokinetics of theophylline (metabolized by CYP1A2) were unaffected. This suggests caution may be warranted when abiraterone is coadministered with known CYP2D6 substrates (including β-blockers,

serotonin reuptake inhibitors, anti-arrhythmics, and neuroleptics, as well as codeine, tramadol, and – of relevance to urologic patients – tolterodine).[87]

Conversely, abiraterone is a substrate of CYP3A4. Interestingly, enzalutamide is a strong inducer of CYP3A4, while ketoconazole and bicalutamide are inhibitors of CYP3A4. Clinical trials evaluating the impact of rifampin (another strong inducer of CYP3A4) on abiraterone exposure (NCT01655147),[88] as well as the impact of ketoconazole on prolonging abiraterone exposure (NCT01588782)[89] have been completed but not yet reported. This suggests that the combination of bicalutamide and abiraterone merits clinical evaluation.

Current place of abiraterone in CRPC therapy

A number of clinical trials evaluating the sequence and combination of abiraterone with immunotherapy, chemotherapy, enzalutamide, and other novel agents are underway in men with metastatic CRPC. While the optimal place of abiraterone in prostate cancer therapy remains to be determined, current treatment decisions can be guided in part by Phase III data already available.

In men with asymptomatic or minimally symptomatic metastatic CRPC, abiraterone is an attractive first-line option given its ease of administration and relatively low toxicity profile. Similarly, the combination of abiraterone and sipuleucel T would likely be a well-tolerated regimen in this setting and is currently under clinical investigation (NCT01487863).[90]

The efficacy of abiraterone in men with symptomatic disease prior to chemotherapy has not been specifically demonstrated due to exclusion of these patients from the Phase III trial. The pace of disease may be the best guide to therapy in this setting. Patients with high Gleason scores, poor response to initial ADT, rapidly progressive disease, or poorly controlled symptoms may derive greater benefit from immediate chemotherapy, while a trial of abiraterone may be reasonable in patients with less extensive or more slowly progressing disease.[91]

In the post-chemotherapy setting, both abiraterone and enzalutamide are supported by Phase III data demonstrating an OS benefit, but the optimal approach to sequencing them is unknown. Retrospective evaluations of patients receiving abiraterone after enzalutamide or vice versa have shown modest response rates with a median TTP of 3–4 months.[92–94] Until biomarkers to stratify patients or clinical trial data to support combination or sequencing strategies are available, the sequencing of abiraterone and enzalutamide is likely to be dictated by insurance and regulatory approvals. From a practical perspective, enzalutamide avoids the need for prednisone, although this may become less important if studies show abiraterone can be given with lower doses of prednisone (NCT01867710).[95]

Cross-resistance with taxanes

An emerging consideration is whether therapy with abiraterone (or enzalutamide) may influence the efficacy of subsequent chemotherapy. Taxanes have been demonstrated to mediate some of their anti-tumor activity in prostate cancer via inhibition of AR transcriptional activity. This has been proposed to occur by various mechanisms including taxane-mediated induction of AR transcriptional corepressors and prevention of microtubule-mediated transit of AR to the nucleus.[92,96,97]

These data suggest the prostate-specific component of taxane efficacy may be lost in tumors that have developed resistance to AR pathway inhibition. Consistent with this hypothesis, a study reported in abstract form found that metastatic CRPC patients who had early development of castration resistance (<12 months) had a shorter TTP and shorter OS compared to patients with more prolonged sensitivity to androgen axis suppression.[98]

A published analysis of the efficacy of docetaxel in patients who had progressed on the Phase I/II studies of abiraterone showed >50% PSA declines in only 26% of patients compared to 45% in the TAX 327 study.[99] Moreover, all patients who had failed to achieve a PSA response on abiraterone were also refractory to docetaxel. A second study reported in abstract form found median OS from the first dose of docetaxel to be 65 months in patients treated with abiraterone or enzalutamide after salvage cabazitaxel therapy, but only 39 months in those receiving these agents after docetaxel but before cabazitaxel.[100] At present these observations remain hypothesis generating.

Mechanisms of resistance to abiraterone

Although clinical responses to abiraterone have been impressive, not all men respond, the duration of response is variable, and a majority eventually progress with a rising PSA. While the mechanisms determining resistance to abiraterone have not been fully elucidated, emerging data from clinical and preclinical studies suggest several possibilities.

Clinical data demonstrate that abiraterone effectively suppresses serum androgens.[63,64] In addition, higher levels of

AR and CYP17A staining in pretreatment tumor-infiltrated bone marrow biopsies from men with CRPC were associated with longer responses to abiraterone treatment, supporting CYP17A mediated androgen production as the target of abiraterone activity.[41] However, the efficacy of abiraterone in suppressing tumor androgens in men with CRPC remains to be demonstrated. In this regard, preclinical studies have provided the first in vivo evidence that the primary mechanism of action of abiraterone is via suppression of tumor androgen levels. Treatment of CRPC xenograft models with abiraterone significantly inhibited tumor growth, serum PSA, and intratumoral androgen levels.[101,102] While androgen levels remained suppressed in some tumors recurring after therapy, other tumors demonstrated increasing levels of T and DHT.

Importantly, multiple mechanisms directed at maintaining AR signaling were observed in the abiraterone-treated tumors. These included upregulated expression of full-length AR and ligand-independent AR variants, as well as induction of steroidogenic genes (including the target gene, *CYP17A*), several of which showed strong correlations with DHT levels in recurrent tumors.[101,102] Clinically, development of resistance to abiraterone has not been associated with an increase in serum androgen levels or in bone marrow aspirate T levels (which contrasts with the increase in circulating adrenal androgens that is seen in men progressing on ketoconazole).[71] However, numerous studies have shown that serum is not a good indicator of tumor androgen levels.[6,103]

Abiraterone withdrawal syndrome

Other potential mechanisms of resistance include activation of mutant AR by noncanonical ligands. Interestingly, recent case reports describe instances of an "abiraterone withdrawal syndrome", in which (generally transient) PSA declines occur following discontinuation of abiraterone.[104–106] To date, abiraterone has not been found to elicit AR agonist activity (as is seen following treatment with AR antagonists such as bicalutamide, flutamide, and now enzalutamide),[37,107] perhaps because it is a relatively weak AR antagonist.[57] An alternative explanation is the development of AR mutations which allow AR activation by exogenous corticosteroids or steroid precursors upstream of CYP17A.

In particular, inhibition of CYP17A is associated with a rise in circulating levels of upstream progesterone precursors,[63,64] which have been shown to activate AR bearing certain mutations.[31,57] Notably, a Phase II study of single-agent abiraterone found that initiation of dexamethasone at progression (to decrease ACTH-driven stimulation of steroid precursors) reversed resistance in 33% of evaluable patients (although this could also reflect an intrinsic anti-tumor activity of dexamethasone).[72] In contrast, however, the exogenous glucocorticoids or mineralocorticoid antagonists used to ameliorate the side effects of abiraterone may themselves be able to activate mutant AR.[35] Alternatively, signaling via the glucocorticoid receptor has been shown to activate AR-regulated genes in the absence of ligand,[108] suggesting another route by which discontinuation of therapy could lead to a withdrawal response.

While further study is clearly needed, these findings are collectively consistent with the clinical observation that patients progress on abiraterone with a rising PSA, strongly suggesting that the AR axis remains a critical target in abiraterone-resistant tumors.

Conclusion and future directions

Many important questions regarding the use of abiraterone remain to be answered including optimal dosing strategies, its role in different disease settings (eg, castration sensitive, biochemically recurrent, or localized disease), and – in all disease settings – whether abiraterone in sequential or combinatorial treatment strategies will yield the most durable responses.

Both clinical and preclinical data suggest abiraterone-resistance is associated with reactivation of AR signaling. That the AR and a second enzyme involved in androgen synthesis (3β-hydroxysteroid dehydrogenase) are inhibited by higher concentrations of abiraterone suggests dose escalation may be a viable strategy to target AR-related mechanisms of abiraterone resistance. This concept is currently under evaluation in two studies of men with metastatic CRPC (NCT01503229, NCT01637402).[109,110]

The persistent AR activation in abiraterone-resistant tumors also provides a compelling rationale for combining abiraterone with potent AR inhibitors such as enzalutamide or ARN-509 rather than sequential treatment strategies which may allow alternative pathways of AR activation to emerge. Although historic studies of combined androgen blockade have yielded small gains in OS versus ADT alone, the markedly more potent drug combinations now available hold significant promise for increasing the efficacy of multi-targeted AR pathway blockade. Studies evaluating the combination of abiraterone and enzalutamide or ARN-509 in men with metastatic CRPC (NCT01650194, NCT01949337, NCT01792687)[111–113] as well as in men with localized disease prior to prostatectomy (NCT01946165)[114] are planned or ongoing.

Early use of abiraterone or potent combined AR blockade may be particularly effective in hormone-naïve tumors which

have not yet had the opportunity to develop resistance. The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study is an ongoing trial comparing ADT with and without abiraterone in high-risk patients with biochemical recurrence or newly diagnosed metastatic patients (NCT00268476),[115] as are several others (NCT01715285).[116] Other studies are evaluating the efficacy of abiraterone and ADT in combination with salvage radiotherapy for biochemical recurrence following prostatectomy (NCT01780220).[117]

Similarly, the efficacy of abiraterone is being explored in combination with prostatectomy or radiotherapy in men with localized disease (NCT01023061, NCT01717053, NCT01751451).[118–120] In this regard, neoadjuvant studies of multi-targeted AR blockade using LH-releasing hormone agonists combined with bicalutamide, dutasteride, and ketoconazole or LH-releasing hormone agonists combined with abiraterone have demonstrated higher pathologic response rates than previously observed in historic studies of ADT prior to prostatectomy.[121,122]

While the limited number of studies reported to date have identified AR-related mechanisms of resistance to abiraterone, it is likely that other signaling and survival pathways will also be found to play important roles in determining response and resistance. As such, numerous studies evaluating the combination of abiraterone with cytotoxic chemotherapy and targeted agents such as dasatinib (Src inhibitor), veliparib (PARP inhibitor), cabozantinib (c-Met and VEGFR2 inhibitor), alisertib (aurora kinase inhibitor), OGX-427 (HSP27 inhibitor), AT13387 (HSP90 inhibitor), BKM120 (PI3K inhibitor), BEZ235 (dual PI3K/mTOR inhibitor), and ABT-264 (Bcl-2 inhibitor) are planned or underway.

In conclusion, numerous studies evaluating the sequencing and combination of abiraterone in multiple disease settings are underway. Rapid accrual and completion of these studies will be imperative for determining rational treatment strategies with the highest likelihood of durable efficacy. Furthermore, the molecular heterogeneity that characterizes CRPC tumors combined with the growing number of oncogenic drivers for which targeted agents are being developed highlights the critical need for embedding correlative studies within these studies and pursuing the development of predictive biomarkers.

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References

1. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. *J Clin Oncol*. 2005;23(32):8253–8261.
2. Geller J, Liu J, Albert J, Fay W, Berry CC, Weis P. Relationship between human prostatic epithelial cell protein synthesis and tissue dihydrotestosterone level. *Clin Endocrinol (Oxf)*. 1987;26(2):155–161.
3. Mohler JL, Gregory CW, Ford OH 3rd, et al. The androgen axis in recurrent prostate cancer. *Clin Cancer Res*. 2004;10(2):440–448.
4. Nishiyama T, Hashimoto Y, Takahashi K. The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue of patients with prostate cancer. *Clin Cancer Res*. 2004;10(21):7121–7126.
5. Page ST, Lin DW, Mostaghel EA, et al. Persistent intraprostatic androgen concentrations after medical castration in healthy men. *J Clin Endocrinol Metab*. 2006;91(10):3850–3856.
6. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res*. 2008;68(11):4447–4454.
7. Culig Z, Hoffmann J, Erdel M, et al. Switch from antagonist to agonist of the androgen receptor bicalutamide is associated with prostate tumour progression in a new model system. *Br J Cancer*. 1999;81(2):242–251.
8. Gregory CW, Johnson RT Jr, Mohler JL, French FS, Wilson EM. Androgen receptor stabilization in recurrent prostate cancer is associated with hypersensitivity to low androgen. *Cancer Res*. 2001;61(7):2892–2898.
9. Gregory CW, Hamil KG, Kim D, et al. Androgen receptor expression in androgen-independent prostate cancer is associated with increased expression of androgen-regulated genes. *Cancer Res*. 1998;58(24):5718–5724.
10. Mohler JL, Morris TL, Ford OH 3rd, Alvey RF, Sakamoto C, Gregory CW. Identification of differentially expressed genes associated with androgen-independent growth of prostate cancer. *Prostate*. 2002;51(4):247–255.
11. Scher HI, Buchanan G, Gerald W, Butler LM, Tilley WD. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. *Endocr Relat Cancer*. 2004;11(3):459–476.
12. Labrie F, Belanger A, Simard J, Luu-The V, Labrie C. DHEA and peripheral androgen and estrogen formation: intracinology. *Ann N Y Acad Sci*. 1995;774:16–28.
13. Locke JA, Wasan KM, Nelson CC, Guns ES, Leon CG. Androgen-mediated cholesterol metabolism in LNCaP and PC-3 cell lines is regulated through two different isoforms of acyl-coenzyme A: cholesterol acyltransferase (ACAT). *Prostate*. 2008;68(1):20–33.
14. Locke JA, Guns ES, Lubik AA, et al. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. *Cancer Res*. 2008;68(15):6407–6415.
15. Leon CG, Locke JA, Adomat HH, et al. Alterations in cholesterol regulation contribute to the production of intratumoral androgens during progression to castration-resistant prostate cancer in a mouse xenograft model. *Prostate*. 2010;70(4):390–400.
16. Mostaghel EA, Solomon KR, Pelton K, Freeman MR, Montgomery RB. Impact of circulating cholesterol levels on growth and intratumoral androgen concentration of prostate tumors. *PLoS One*. 2012;7(1):e30062.
17. Stanbrough M, Bubley GJ, Ross K, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Res*. 2006;66(5):2815–2825.

18. Hofland J, van Weerden WM, Dits NF, et al. Evidence of limited contributions for intratumoral steroidogenesis in prostate cancer. *Cancer Res*. 2010;70(3):1256–1264.
19. Bubendorf L, Kononen J, Koivisto P, et al. Survey of gene amplifications during prostate cancer progression by high-throughout fluorescence in situ hybridization on tissue microarrays. *Cancer Res*. 1999;59(4):803–806.
20. Ford OH 3rd, Gregory CW, Kim D, Smitherman AB, Mohler JL. Androgen receptor gene amplification and protein expression in recurrent prostate cancer. *J Urol*. 2003;170(5):1817–1821.
21. Linja MJ, Savinainen KJ, Saramaki OR, Tammela TLJ, Vessella RL, Visakorpi T. Amplification and overexpression of androgen receptor gene in hormone-refractory prostate cancer. *Cancer Res*. 2001;61(9):3550–3555.
22. Visakorpi T, Hyytinen E, Koivisto P, et al. In vivo amplification of the androgen receptor gene and progression of human prostate cancer. *Nat Genet*. 1995;9(4):401–406.
23. van der Kwast TH, Schalken J, Ruizeveld de Winter JA, et al. Androgen receptors in endocrine-therapy-resistant human prostate cancer. *Int J Cancer*. 1991;48(2):189–193.
24. Ruizeveld de Winter JA, Janssen PJ, Sleddens HM, et al. Androgen receptor status in localized and locally progressive hormone refractory human prostate cancer. *Am J Pathol*. 1994;144(4):735–746.
25. Taplin ME, Bubley GJ, Shuster TD, et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Engl J Med*. 1995;332(21):1393–1398.
26. Holzbeierlein J, Lal P, LaTulippe E, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. *Am J Pathol*. 2004;164(1):217–227.
27. Latil A, Bieche I, Vidaud D, et al. Evaluation of androgen, estrogen (ER alpha and ER beta), and progesterone receptor expression in human prostate cancer by real-time quantitative reverse transcription-polymerase chain reaction assays. *Cancer Res*. 2001;61(5):1919–1926.
28. Miyamoto H, Rahman MM, Chang C. Molecular basis for the antiandrogen withdrawal syndrome. *J Cell Biochem*. 2004;91(1):3–12.
29. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. *Nat Med*. 2004;10(1):33–39.
30. Brooke GN, Bevan CL. The role of androgen receptor mutations in prostate cancer progression. *Curr Genomics*. 2009;10(1):18–25.
31. Culig Z, Hobisch A, Cronauer MV, et al. Mutant androgen receptor detected in an advanced-stage prostatic carcinoma is activated by adrenal androgens and progesterone. *Mol Endocrinol*. 1993;7(12):1541–1550.
32. Tan J, Sharief Y, Hamil KG, et al. Dehydroepiandrosterone activates mutant androgen receptors expressed in the androgen-dependent human prostate cancer xenograft CWR22 and LNCaP cells. *Mol Endocrinol*. 1997;11(4):450–459.
33. Taplin ME. Drug insight: role of the androgen receptor in the development and progression of prostate cancer. *Nat Clin Pract Oncol*. 2007;4(4):236–244.
34. Yuan X, Balk SP. Mechanisms mediating androgen receptor reactivation after castration. *Urol Oncol*. 2009;27(1):36–41.
35. Zhao XY, Malloy PJ, Krishnan AV, et al. Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. *Nat Med*. 2000;6(6):703–706.
36. Steinkamp MP, O'Mahony OA, Brogley M, et al. Treatment-dependent androgen receptor mutations in prostate cancer exploit multiple mechanisms to evade therapy. *Cancer Res*. 2009;69(10):4434–4442.
37. Korpal M, Korn JM, Gao X, et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). *Cancer Discov*. 2013;3(9):1030–1043.
38. Balbas MD, Evans MJ, Hosfield DJ, et al. Overcoming mutation-based resistance to antiandrogens with rational drug design. *Elife*. 2013;2:e00499.
39. Joseph JD, Lu N, Qian J, et al. A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509. *Cancer Discov*. 2013;3(9):1020–1029.
40. Guo Z, Yang X, Sun F, et al. A novel androgen receptor splice variant is up-regulated during prostate cancer progression and promotes androgen depletion-resistant growth. *Cancer Res*. 2009;69(6):2305–2313.
41. Hu R, Dunn TA, Wei S, et al. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. *Cancer Res*. 2009;69(1):16–22.
42. Zhao JJ, Lin J, Lwin T, et al. microRNA expression profile and identification of miR-29 as a prognostic marker and pathogenetic factor by targeting CDK6 in mantle cell lymphoma. *Blood*. 2010;115(13):2630–2639.
43. Hornberg E, Ylitalo EB, Crnalic S, et al. Expression of androgen receptor splice variants in prostate cancer bone metastases is associated with castration-resistance and short survival. *PLoS One*. 2011;6(4):e19059.
44. Haile S, Sadar MD. Androgen receptor and its splice variants in prostate cancer. *Cell Mol Life Sci*. 2011;68(24):3971–3981.
45. Greenberg E. Endocrine therapy in the management of prostatic cancer. *Clin Endocrinol Metab*. 1980;9(2):369–381.
46. Robinson MR, Shearer RJ, Fergusson JD. Adrenal suppression in the treatment of carcinoma of the prostate. *Br J Urol*. 1974;46(5):555–559.
47. Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer*. 2002;95(2):361–376.
48. Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer [review]. *Cochrane Database Syst Rev*. 2000;2:CD001526.
49. Caubet JF, Tosteson TD, Dong EW, et al. Maximum androgen blockade in advanced prostate cancer: a meta-analysis of published randomized controlled trials using nonsteroidal antiandrogens. *Urology*. 1997;49(1):71–78.
50. Small EJ, Ryan CJ. The case for secondary hormonal therapies in the chemotherapy age. *J Urol*. 2006;176(6 Pt 2):S66–S71.
51. de Bono JS, Logothetis CJ, Fizazi K, et al. Abiraterone acetate (AA) plus low dose prednisone (P) improves overall survival (OS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after docetaxel-based chemotherapy (chemo): results of COU-AA-301, a randomized double-blind placebo-controlled Phase III study [abstract]. *Ann Oncol*. 2010;21(Suppl 8):LBA5.
52. Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a Phase I–II study. *Lancet*. 2010;375(9724):1437–1446.
53. Efstathiou E, Titus M, Tsavachidou D, et al. Effects of abiraterone acetate on androgen signaling in castrate-resistant prostate cancer in bone. *J Clin Oncol*. 2012;30(6):637–643.
54. Handratta VD, Vasaitis TS, Njar VC, et al. Novel C-17-heteroaryl steroidal CYP17 inhibitors/antiandrogens: synthesis, in vitro biological activity, pharmacokinetics, and antitumor activity in the LAPC4 human prostate cancer xenograft model. *J Med Chem*. 2005;48(8):2972–2984.
55. Rowlands MG, Barrie SE, Chan F, et al. Esters of 3-pyridylacetic acid that combine potent inhibition of 17 alpha-hydroxylase/C17,20-lyase (cytochrome P45017 alpha) with resistance to esterase hydrolysis. *J Med Chem*. 1995;38(21):4191–4197.
56. Attard G, Reid AH, Auchus RJ, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. *J Clin Endocrinol Metab*. 2012;97(2):507–516.
57. Richards J, Lim AC, Hay CW, et al. Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor: a rationale for increasing abiraterone exposure or combining with MDV3100. *Cancer Res*. 2012;72(9):2176–2182.
58. Soifer HS, Souleimanian N, Wu S, et al. Direct regulation of androgen receptor activity by potent CYP17 inhibitors in prostate cancer cells. *J Biol Chem*. 2012;287(6):3777–3787.

59. Eil C. Ketoconazole binds to the human androgen receptor. *Horm Metab Res*. 1992;24(8):367–370.
60. Li R, Evaul K, Sharma KK, et al. Abiraterone inhibits 3β-hydroxysteroid dehydrogenase: a rationale for increasing drug exposure in castration-resistant prostate cancer. *Clin Cancer Res*. 2012;18(13):3571–3579.
61. Barrie SE, Potter GA, Goddard PM, Haynes BP, Dowsett M, Jarman M. Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17–20 lyase). *J Steroid Biochem Mol Biol*. 1994;50(5–6):267–273.
62. O'Donnell A, Judson I, Dowsett M, et al. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. *Br J Cancer*. 2004;90(12):2317–2325.
63. Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563–4571.
64. Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol*. 2010;28(9):1481–1488.
65. Todd M, Meyers ML, Charnas R, Acharya M, Molina A. Fast and flawed or scientifically sound: the argument for administering oral oncology drugs during fasting. *J Clin Oncol*. 2012;30(8):888–889.
66. Janssen-Ortho Inc., Canada. A Study to Determine the Short-Term Safety of Continuous Dosing of Abiraterone Acetate and Prednisone in Modified Fasting and Fed States to Patients With Metastatic Castration-Resistant Prostate Cancer. Available from: http://clinicaltrials.gov/show/NCT01424930. NLM identifier: NCT01424930. Accessed December 10, 2013.
67. University of Chicago. Food Effect Study of Abiraterone Acetate for Treatment of Patients With Castration-Resistant Prostate Cancer. Available from: http://clinicaltrials.gov/show/NCT01543776. NLM identifier: NCT01543776. Accessed December 10, 2013.
68. Ratain MJ. Flushing oral oncology drugs down the toilet. *J Clin Oncol*. 2011;29(30):3958–3959.
69. Marbury T, Stonerock R, Tran N, Gonzalez M. A Phase I single dose open-label reduced/staged pharmacokinetic (PK) and safety study of abiraterone acetate (AA) in men with imapired renal function. *Eur J Cancer*. 2011;47(Suppl 1):S502.
70. Acharya M, Gonzalez M, Mannens G, et al. A Phase I, open-label, single-dose, mass balance study of 14C-labeled abiraterone acetate in healthy male subjects. *Xenobiotica*. 2013;43(4):379–389.
71. Ryan CJ, Halabi S, Ou SS, Vogelzang NJ, Kantoff P, Small EJ. Adrenal androgen levels as predictors of outcome in prostate cancer patients treated with ketoconazole plus antiandrogen withdrawal: results from a cancer and leukemia group B study. *Clin Cancer Res*. 2007;13(7):2030–2037.
72. Attard G, Reid AH, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J Clin Oncol*. 2009;27(23):3742–3748.
73. Ryan CJ, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res*. 2011;17(14):4854–4861.
74. Reid AH, Attard G, Danila DC, et al. Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. *J Clin Oncol*. 2010;28(9):1489–1495.
75. Danila DC, Morris MJ, de Bono JS, et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J Clin Oncol*. 2010;28(9):1496–1501.
76. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled Phase III study. *Lancet Oncol*. 2012;13(10):983–992.
77. Goodman OB, Flaig TW, Molina A, et al. Exploratory analysis of the visceral disease (VD) patient subset in COU-AA-301, a Phase III study of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol*. 2013;31(Suppl 6):14.
78. Sternberg CN, Molina A, North S, et al. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. *Ann Oncol*. 2013;24(4):1017–1025.
79. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol*. 2012;13(12):1210–1217.
80. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138–148.
81. Rathkopf DE, Smith MR, De Bono JS, et al. Updated interim analysis (IA) of COU-AA-302, a randomized Phase III study of abiraterone acetate (AA) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) without prior chemotherapy [abstract]. *J Clin Oncol*. 2013;31(Suppl 6):5.
82. Ferraldeschi R, Sharifi N, Auchus RJ, Attard G. Molecular pathways: inhibiting steroid biosynthesis in prostate cancer. *Clin Cancer Res*. 2013;19(13):3353–3359.
83. Pia A, Vignani F, Attard G, et al. Strategies for managing ACTH dependent mineralocorticoid excess induced by abiraterone. *Cancer Treat Rev*. 2013;39(8):966–973.
84. Procopio G, Grassi P, Testa I, et al. Safety of abiraterone acetate in castration-resistant prostate cancer patients with concomitant cardiovascular risk factors. *Am J Clin Oncol*. Epub September 21, 2013.
85. Tolcher AW, Chi KN, Shore ND, et al. Effect of abiraterone acetate plus prednisone on the QT interval in patients with metastatic castration-resistant prostate cancer. *Cancer Chemother Pharmacol*. 2012;70(2):305–313.
86. Chi KN, Tolcher A, Lee P, et al. Effect of abiraterone acetate plus prednisone on the pharmacokinetics of dextromethorphan and theophylline in patients with metastatic castration-resistant prostate cancer. *Cancer Chemother Pharmacol*. 2013;71(1):237–244.
87. Bertilsson L, Dahl ML, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Br J Clin Pharmacol*. 2002;53(2):111–122.
88. Janssen Research and Development, LLC. A Study to Evaluate the Effect of Rifampicin on the Pharmacokinetics of Abiraterone in Healthy Male Participants. Available from: http://clinicaltrials.gov/show/NCT01655147. NLM identifier: NCT01655147. Accessed December 10, 2013.
89. Janssen Research and Development, LLC. A Study to Assess the Effect of Ketoconazole on the Pharmacokinetics of Abiraterone Following Administration of Abiraterone Acetate Tablets in Healthy Adult Men. Available from: http://clinicaltrials.gov/show/NCT01588782. NLM identifier: NCT01588782. Accessed December 10, 2013.
90. Dendreon. Concurrent Versus Sequential Treatment With Sipuleucel-T and Abiraterone in Men With Metastatic Castrate Resistant Prostate Cancer (mCRPC). Available from: http://clinicaltrials.gov/show/NCT01487863. NLM identifier: NCT01487863. Accessed December 10, 2013.
91. Fitzpatrick JM, de Wit R. Taxane mechanisms of action: potential implications for treatment sequencing in metastatic castration-resistant prostate cancer. *Eur Urol*. Epub July 25, 2013.
92. Gan L, Chen S, Wang Y, et al. Inhibition of the androgen receptor as a novel mechanism of taxol chemotherapy in prostate cancer. *Cancer Res*. 2009;69(21):8386–8394.
93. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol*. 2013;24(7):1807–1812.
94. Schrader AJ, Boegemann M, Ohlmann CH, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur Urol*. 2014;65(1):30–36.
95. Janssen Pharmaceutica N.V., Belgium. Abiraterone With Different Steroid Regimens for Side Effect Related to Mineralcorticoid Excess Prevention in Prostate Cancer Prior to Chemotherapy. Available from: http://clinicaltrials.gov/show/NCT01867710. NLM identifier: NCT01867710. Accessed December 10, 2013.

96. Darshan MS, Loftus MS, Thadani-Mulero M, et al. Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. *Cancer Res*. 2011;71(18): 6019–6029.
97. Zhu ML, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. *Cancer Res*. 2010;70(20):7992–8002.
98. Huillard O, Albiges L, Eymard JC, et al. Efficacy of docetaxel chemotherapy in metastatic prostate cancer (mPC) patients (pts) experiencing early castration resistance (CR) [abstract]. *J Clin Oncol*. 2013;31(Suppl):5075.
99. Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Ann Oncol*. 2012;23(11):2943–2947.
100. Angelergues A, Maillet D, Flechon A, et al. Prognostic factors of survival in patients with metastatic castration resistant prostate cancer (mCRPC) treated with cabazitaxel: sequencing might matter [abstract]. *J Clin Oncol*. 2013;31(Suppl):5063.
101. Mostaghel EA, Marck BT, Plymate SR, et al. Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. *Clin Cancer Res*. 2011;17(18):5913–5925.
102. Cai C, Chen S, Ng P, et al. Intratumoral de novo steroid synthesis activates androgen receptor in castration-resistant prostate cancer and is upregulated by treatment with CYP17A1 inhibitors. *Cancer Res*. 2011;71(20):6503–6513.
103. Mostaghel EA, Page ST, Lin DW, et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. *Cancer Res*. 2007;67(10):5033–5041.
104. Caffo O, Palermo A, Veccia A, et al. Biochemical and objective response to abiraterone acetate withdrawal: incidence and clinical relevance of a new scenario for castration-resistant prostate cancer. *Urology*. 2013;82(5):1090–1093.
105. Gauthier H, Bousquet G, Pouessel D, Culine S. Abiraterone acetate withdrawal syndrome: does it exist? *Case Rep Oncol*. 2012;5(2):385–387.
106. Witjes JA. A case of abiraterone acetate withdrawal. *Eur Urol*. 2013;64(3):517–518.
107. Labrie F, Dupont A, Belanger A, et al. New approach in the treatment of prostate cancer: complete instead of partial withdrawal of androgens. *Prostate*. 1983;4(6):579–594.
108. Sahu B, Laakso M, Pihlajamaa P, et al. FoxA1 specifies unique androgen and glucocorticoid receptor binding events in prostate cancer cells. *Cancer Res*. 2013;73(5):1570–1580.
109. University of Washington. Abiraterone Acetate in Treating Patients With Metastatic Hormone-Resistant Prostate Cancer. Available from: http://clinicaltrials.gov/show/NCT01508234. NLM identifier: NCT01503229. Accessed December 10, 2013.
110. Terence Friedlander, MD. A Phase II Study of Increased-Dose Abiraterone Acetate in Patients With Castration Resistant Prostate Cancer. Available from: http://clinicaltrials.gov/show/NCT01637402. NLM identifier: NCT01637402. Accessed December 10, 2013.
111. Astellas Pharma Global Development, Inc. A Study to Determine Safety and Tolerability of Enzalutamide (MDV3100) in Combination With Abiraterone Acetate in Bone Metastatic Castration-Resistant Prostate Cancer Patients. Available from: http://clinicaltrials.gov/show/NCT01650194. NLM identifier: NCT01650194. Accessed December 10, 2013.
112. Alliance for Clinical Trials in Oncology. Enzalutamide With or Without Abiraterone Acetate and Prednisone in Treating Patients With Castration-Resistant Metastatic Prostate Cancer. Available from: http://clinicaltrials.gov/show/NCT01949337. NLM identifier: NCT01949337. Accessed December 10, 2013.
113. Aragon Pharmaceuticals, Inc. Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumor Activity of Ascending Doses of ARN 509 in Combination With Abiraterone Acetate. Available from: http://clinicaltrials.gov/show/NCT01792687. NLM identifier: NCT01792687. Accessed December 10, 2013.
114. M.D. Anderson Cancer Center.Abiraterone Acetate Plus LHRH Agonist and Abiraterone Acetate Plus LHRH Agonist and Enzalutamide. Available from: http://clinicaltrials.gov/show/NCT01946165. NLM identifier: NCT01946165. Accessed December 10, 2013.
115. Medical Research Council.STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomised Controlled Trial. Available from: http://clinicaltrials.gov/show/NCT00268476. NLM identifier: NCT00268476. Accessed December 10, 2013.
116. Janssen Research & Development, LLC. A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Patients With High-Risk, Metastatic Hormone-Naive Prostate Cancer (mHNPC). Available from: http://clinicaltrials.gov/show/NCT01715285. NLM identifier: NCT01715285. Accessed December 10, 2013.
117. UNICANCER. Safety and Efficacy of Radiotherapy Combined With a 6-month LH-RH Agonist and Abiraterone Hormone Therapy Treatment in Biochemically-relapsing Prostate Cancer Following Surgery (CARLHA). Available from: http://clinicaltrials.gov/show/NCT01780220. NLM identifier: NCT01780220. Accessed December 10, 2013.
118. University of Washington. Abiraterone Acetate, Prednisone, and Leuprolide Acetate or Goserelin Before and During Radiation Therapy in Treating Patients With Localized or Locally Advanced Prostate Cancer. Available from: http://clinicaltrials.gov/show/NCT01023061. NLM identifier: NCT01023061. Accessed December 10, 2013.
119. Duke University.Abiraterone, Radiotherapy and Short-Term Androgen Deprivation in Unfavorable Localized Prostate Cancer. Available from: http://clinicaltrials.gov/show/NCT01717053. NLM identifier: NCT01717053. Accessed December 10, 2013.
120. Memorial Sloan-Kettering Cancer Center.3-arm Study of Abiraterone Acetate Alone, Abiraterone Acetate Plus Degarelix, a GnRH Antagonist, and Degarelix Alone for Patients With Prostate Cancer With a Rising PSA or a Rising PSA and Nodal Disease Following Definitive Radical Prostatectomy. Available from: http://clinicaltrials.gov/show/NCT01751451. NLM identifier: NCT01751451. Accessed December 10, 2013.
121. Mostaghel EA, Nelson PS, Lange P, et al. Targeted androgen pathway suppression in localized prostate cancer: a randomized clinical trial. *J Clin Oncol*. Epub 2013 Dec 9.
122. Taplin ME, Montgomery RB, Logothetis C, et al. Effect of neoadjuvant abiraterone acetate (AA) plus leuprolide acetate (LHRHa) on PSA, pathological complete response (pCR), and near pCR in localized high-risk prostate cancer (LHRPC): results of a randomized Phase II study [abstract]. *J Clin Oncol*. 2012;30(Suppl):4521.

EXHIBIT P

Patent Board Grants Inter Partes Review Of Cancer-Fighting Therapy

Mealey's(R) Litigation Report: Patents

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Body

A claimed method and composition for treating cancer with hormone therapy is likely unpatentable under 35 U.S. Code Section 103, the Patent Trial and Appeal Board ruled May 31 in a decision granting inter partes review (***Amerigen*** Pharmaceuticals Ltd. v. ***Janssen Oncology*** Inc., No. IPR2016-00286, PTAB).

(Decision available 16-160606-032Z)

Respondent Janssen Oncology Inc.'s U.S. patent No. 8,822,438 describes administration of an effective amount of 17a-hydroxylase/C17, 20-lyase (CYP17) - an enzyme involved in testosterone synthesis - inhibitor, such as abiraterone acetate, with a steroid like prednisone or dexamethasone to slow the growth of prostate cancer.

According to the PTAB, however, petitioner Amerigen Pharmaceuticals Ltd. is likely correct that the invention would have been obvious in light of prior art identified as "Hormonal Impact of the 17a-hydroxylase/C17, 20-lyase Inhibitor Abiraterone Acetate in Patients with Prostate Cancer" (O'Donnell), "Prostate Specific Antigen for Assessing Response to Ketoconazole and Prednisone in Patients with Hormone Refractory Metastatic Cancer" (Gerber) and U.S. patent No. 5,604,213 (Barrie).

The '438 has been frequently litigated. Although some cases filed by Janssen have been terminated, several others remain active including BTG Int'l Ltd., et al. v. Actavis Labs Fl. Inc,. et al. (C.A. No. 2:15-cv-05909-KM-JBC [D. N.J.]) and Janssen Biotech Inc., et al. v. Mylan Pharm. Inc., et al. (C.A. No. 1:15-cv-00130-IMK [N.D. W. Va.]). Additionally, the '438 patent is the current subject of an ex parte re-examination request. In that proceeding, the request has been assigned to a patent examiner.

Safe, Effective

After adopting the petitioner's proposed construction of claim terms "treat," "treating," "treatment," "anti-cancer agent" and "refractory cancer," the PTAB found that O'Donnell, which discloses the treatment of prostate cancer with abiraterone acetate at a dose of 500-800 mg, combined with Gerber, which discloses the use of ketoconazole to treat patients progressive prostate cancer, would have been obvious to one of ordinary skill in the art.

"We are persuaded, on this record, that the relative success of administration of ketoconazole together with prednisone to treat prostate cancer would lead one of ordinary skill in the art to expect that the 'addition of 10 mg of prednisone daily according to Gerber to the treatment regimen of O'Donnell would be safe and effective in treating a prostate cancer, including prostate cancer refractory to anticancer therapy, including hormone and anti-androgen therapy,'" the PTAB ruled, citing Amerigen's petition.

Similarly, according to the PTAB, a person of ordinary skill in the art would have been motivated to add prednisone to the method taught by Barrie, which is directed to a class of 17-substituted steroids useful in cancer treatment.

"Patent Owner argues that Petitioner's challenges to the claims based on Barrie and Gerber fail for 'all of the same reasons discussed above with respect to the combination of' O'Donnell and Gerber. For the reasons articulated with respect to the combination of O'Donnell and Gerber, above, we are not persuaded by Patent Owner's arguments," the PTAB concluded.

Counsel

Amerigen is represented by William Hare and Gabriela Materassi of McNeeley, Hare & War in Washington.

Dianne B. Elderkin, Barbara L. Mullin and Ruben H. Munoz of Akin, Gump, Strauss, Hauer & Feld in Philadelphia represent Janssen.

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EXHIBIT Q

United States: PTAB Institutes Separate IPR Proceedings Filed By Codefendants, Finding That The Later IPR Proceeding Was Not Barred By 35 U.S.C. § 325(d), PTAB Litigation Blog

Mondaq Business Briefing

February 7, 2017 Tuesday

Length: 620 words

Byline: Dr. Cary Miller Ph.D. and Kunyong Yang

Body

On January 19, 2017, the PTAB instituted inter partes review of U.S. Patent No. 8,822,438 ("the '438 patent") filed by Wockhardt Bio AG ("***Wockhardt***") (IPR2016-01582). The '438 patent is owned by ***Janssen Oncology***, Inc. ("Janssen") and is the subject of several ongoing inter partes reviews, one of which was filed by Amerigen Pharm., Inc. ("Amerigen") which was instituted on May 31, 2016 (IPR2016-00286). The '438 patent is also being asserted in several district court proceedings against Amerigen, Wockhardt and other defendants.

The '438 patent describes methods for treating hormone sensitive cancers with CYP17 inhibitors such as abiraterone acetate in combination with steroids such as prednisone or dexamethasone. Claim 1 recites:

1. A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.

Wockhardt challenged claims 1-20 of the '438 patent as obvious over several references. Janssen did not specifically address the obviousness arguments in its responses. As such, the PTAB was persuaded by Wockhardt's obviousness arguments and instituted the IPR.

Rather than addressing Wockhardt's obviousness arguments, Janssen mainly argued that: (A) the IPR petition should be denied because Wockhardt failed to identify Amerigen as a real party-in-interest; and (B) the IPR should be denied under 35 U.S.C. § 325(d) since it presented the same prior art and substantially the same arguments as the previously instituted Amerigen IPR. The PTAB rejected Janssen's arguments on both grounds.

Regarding the real party-in-interest issue, Janssen argued that Wockhardt and Amerigen are more than just codefendants in a patent lawsuit related to the '438 patent. Although the content and discussion of the evidence provided by Janssen are redacted from the decision, the PTAB, in rejecting Janssen's argument at this time, emphasized that "[a]lthough we may consider the relationship between the parties, the focus of our real party-in-interest inquiry is the relationship between a party and a proceeding."

Regarding the § 325(d) issue, while acknowledging that the instant IPR and the Amerigen IPR assert similar challenges to patentability based on some of the same prior art, the PTAB pointed out that Wockhardt's IPR petition

includes new references, it uses different expert declarants, and noted the parties may make different arguments about secondary considerations of non-obviousness. In the end, the PTAB refused to exercise its discretion under 35 U.S.C. § 325(d) to decline the instant IPR stating that Wockhardt is not attempting to get "a second bite at the apple by an identical petitioner" and it is not seeking to cure any problems in the Amerigen IPR since the Amgerigen IPR was granted. While it instituted the IPR, the PTAB has implemented a condensed schedule in order to decide the instant IPR around the same time as the Amerigen IPR.

The decision emphasizes the importance the PTAB places on establishing a relationship between a party and an IPR proceeding when determining whether the party is a real party-in-interest. The decision also illustrates that the PTAB has broad discretion as to whether to decline an IPR petition under 35 U.S.C. § 325(d) as duplicative.

The content of this article is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

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EXHIBIT R

Zytiga To Face Challenges

Business Monitor Online

November 3, 2016 Thursday

BMI Research
A FitchGroup Company

Length: 1282 words

Highlight: With Zytiga facing generic competition and increased pressures from Xtandi, revenues from Johnson &;#038; Johnson's drug will begin falling. While there have been trials of new formulations, and dosing with standardised diets, no labelling update is likely to occur. J&;#038;J's focus will be on apalutamide, which will be a direct competitor to Xtandi. In addition, combinations with Zytiga will prolong the earning life of the older drug.

Body

BMI View: With Zytiga facing generic competition and increased pressures from Xtandi, revenues fromJohnson & Johnson'sdrugwillbegin falling. While there have been trialsofnew formulations, and dosing with standardised diets, no labelling update is likely to occur. J&J's focus will be on apalutamide, which will be a direct competitor to Xtandi. In addition, combinations with Zytiga will prolong the earning life of theolderdrug.Zytiga (abiraterone acetate) is a growth driver for **Johnson & Johnson**, being one of the company's highest revenue earners, with USD2.2bn recorded in FY2015, and in Q316, sales rose 5.3% worldwide highlighting continued growth in FY16. As an orally available tablet, it has approvals in the US and EU, and first entered the market in 2011.

Zytiga US/EU Approvals

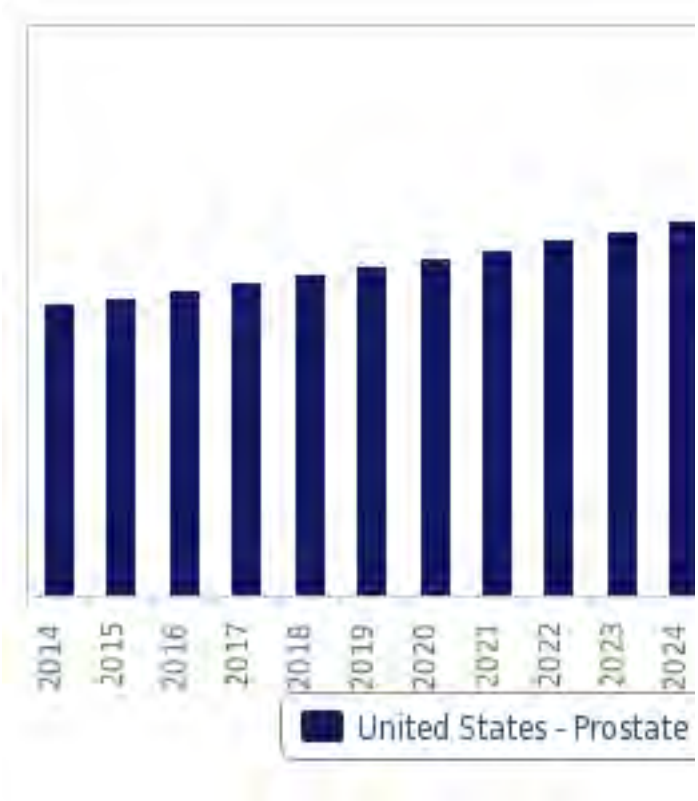
Region	Indication	Approval Date
US	Combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel	April 28 2011
US	New Indication: Combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer	December 12 2012
US	Efficacy labelling change with clinical data	March 20 2015
EU	Combination with prednisone or prednisolone, for the treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen	September 5 2011
EU	Combination with prednisone or prednisolone, for the treatment of metastatic castration-resistant prostate cancer, in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated	January 25 2013

Source: FDA, EMA **Prostate Cancer Represented High Growth Target** At the time J&J acquired *Zytiga,* with the purchase of **Cougar Pharmaceuticals** in May 2009, the prostate cancer market was underpenetrated and J&J was able to enter a relatively competition-free market. However the metastatic castration-resistant prostate cancer market, once one with few options for patients, is now gaining momentum. Since 2010, numerous drugs have

received approval; in addition to *Zytiga*, notably **Sanofi**'s *Jevtana* (cabazitaxel) in June 2010 and **Astellas Pharma**/ **Medivation** (**Pfizer**)'s *Xtandi* (enzalutamide) in August 2012. Prostate cancer represents a sizeable opportunity. According to the National Institutes of Health, prostate cancer represents 10.7% of all new cancer cases in the US, and there will be an estimated 180,890 new cases in 2016, and deaths will stand at 4.4% of total cancer deaths. According to **BMI**'s Disease Database, disability adjusted life years lost to prostate cancer in the US is expected to rise from 660,083 in 2015, to 962,918 by 2030.

Prostate Cancer Burden Growing

US Prostate Cancer DALYs



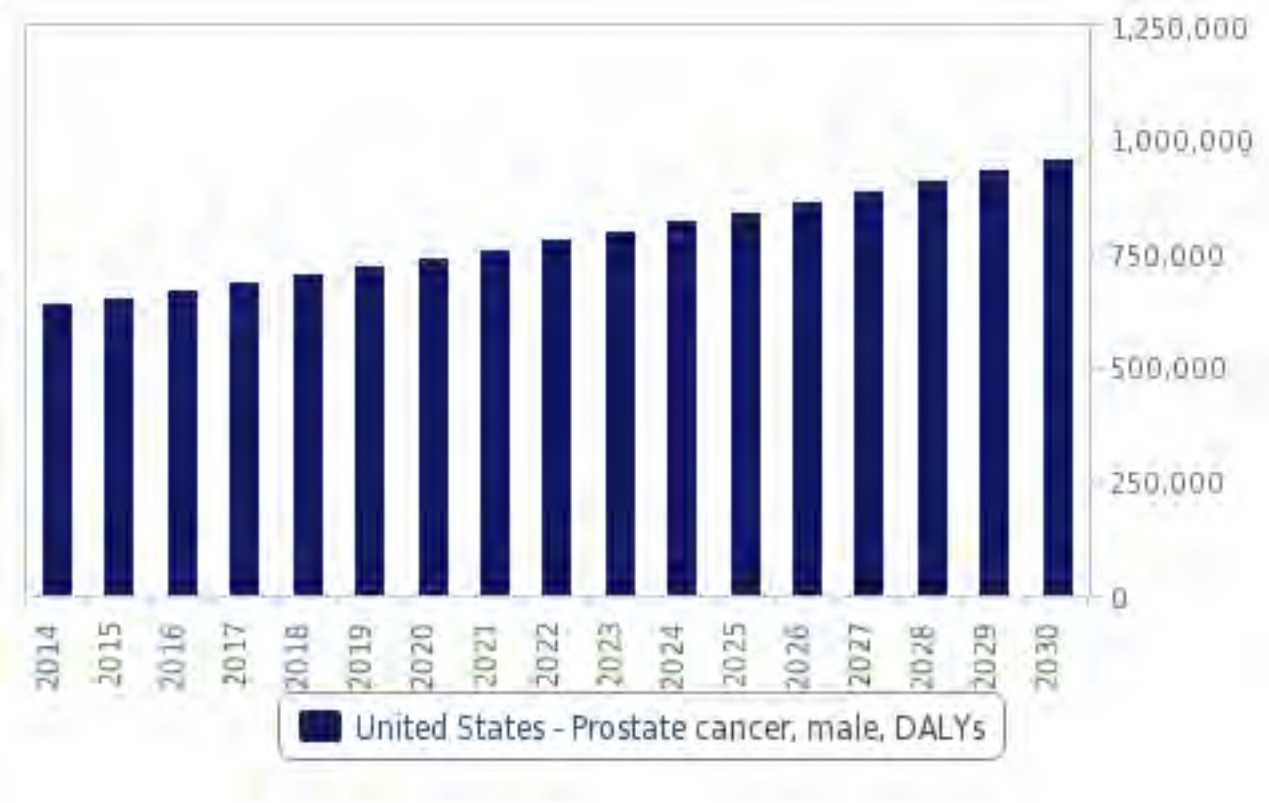
Source: World Health Organization (WHO)/ BMI

Competition Threatens Market Leadership After the launch of *Zytiga*, J&J quickly took a leading share of the prostate cancer market. However, the launch of *Xtandi* in 2013 placed pressure on J&J. Other competitors were not approved for first-line treatment, and this significantly improved *Zytiga*'s position. *Zytiga* has lost market share in the US to *Xtandi* while still recording increasing sales; however, this has been offset by further growth outside of the US. *Zytiga*'s revenues will remain static in the short-term due to *Xtandi* taking market share and will begin to erode in the longer term as generic competition is expected.

Xtandi Revenues Overtake Zytiga

Zytiga/Xtandi Sales (USDmn), 2011-2019

Zytiga To Face Challenges



Note: Astellas ' fiscal year runs from April 1 to March 31. Medivation/Pfizer revenues for Xtandi relate to collaboration revenues. F = forecast. Source: Bloomberg

Food Restrictions LimitZytiga'sPotential*Xtandi* has benefitted from *Zytiga*'s limitations. *Zytiga* must be taken with the concomitant corticosteroid, prednisone, and must be taken on an empty stomach, whereas *Xtandi* does not require prednisone and can be taken with or without food. However, J&J has been conducting trials to improve its product. The current food restrictions are due to highly variable exposure to the drug when eaten with meals containing varying fat content. Trials sponsored by **Janssen** (J&J) on clinicaltrials.gov are investigating coated versus uncoated tablets, while still in fasted conditions, and standardised diets. These trials have been completed, but J&J has not widely released results and no new formulations of *Zytiga* have entered the company's published pipeline. *Zytiga* is a white oval tablet that is 15.9mm by 9.5mm in size. This is compared with *Xtandi* capsules that are 20mm by 9mm. These are fairly large tablets that could pose issues for patients with trouble swallowing. However, oral formulations can be favourable over injections and infusions that require healthcare facility visits.

Zytiga And Xtandi Specifications

	Zytiga	**Xtandi**
Formulation	Oral; tablet	Oral; capsule
Dosing	1,000mg (4 x 250mg) administered orally once daily in combination with prednisone 5mg administered orally twice daily	160mg (4 x 40mg) once daily
Method of Administration	Not to be taken with food, at least two hours after eating, and no food one hour after taking Zytiga	Can be taken with or without food
Size	15.9mm x 9.5mm	20mm x 9mm
Average US List Price Per Year	USD92,092	USD129,000

Zytiga To Face Challenges

	Zytiga	Xtandi
Shelf Life	Two years	Three years
Storage	Store below 30degC	No special storage conditions

Source: BMI **Generic Competition Emerging** Notably, a number of ANDAs have been filed for *Zytiga*, and these have initiated a patent challenge. ***Mylan*** is being sued by **BTG International**, **Janssen Biotech**, ***Janssen Oncology*** and **JanssenResearch & Development** in connection with the filing of an ANDA for a generic 250mg abiraterone tablet product. Mylan believes that it is one of the first companies to have filed a substantially complete ANDA with a Paragraph IV certification for the product, and thus may be eligible for the 180-day generic marketing exclusivity provision allowed under the Hatch-Waxman Act. The lawsuit against Mylan has been filed in the US District Court for the District of New Jersey. Mylan is the second company to have recently announced it has filed an ANDA for a proposed generic version of *Zytiga*. In August 2015, **Hikma Pharmaceuticals** announced it had filed an ANDA for a generic version of *Zytiga.* In response, on July 31 2015, BTG International, Janssen Biotech and various other Janssen affiliates filed a patent infringement lawsuit against Hikma in the US District Court for the District of New Jersey. *Zytiga* is protected by two patents listed in the FDA's Orange Book. These are US Patent Nos. 5,604,213, which is scheduled to expire on December 13 2016; and 8,822,438, which is scheduled to expire on August 24 2027. In addition, *Zytiga* was protected by two periods of data exclusivity. The first, covering the use of the drug in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer, which expired on December 10 2015. The second was a new chemical entity period of data exclusivity, which expired on April 28 2016. **Express Scripts** is expecting generic *Zytiga* in October 2018, despite patent protection until 2027. J&J does have a follow-on product in Phase III trials, apalutamide, which could offset any *Zytiga* losses. Apalutamide is a potent next-generation androgen receptor antagonist. It is a non-steroidal anti-androgen, similar to *Xtandi*. If approved, apalutamide will be a significant competitor for *Xtandi*. It is being trialled as a single agent and in combination with *Zytiga,* which will aid in tempering revenue losses.

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REPORT

How Drug Life-Cycle Management Patent Strategies May Impact Formulary Management

Jan Berger, MD, MJ; Jeffrey D. Dunn, PharmD, MBA; Margaret M. Johnson, BS, RPh; Kurt R. Karst, JD; and W. Chad Shear, JD

This article is based on discussions from a recent roundtable meeting that focused on how drug life-cycle management patent strategies affect the decision-making process regarding formulary planning and management strategies when single-source, branded oral pharmaceutical products transition from single-source to generic status in the United States. The roundtable participants also explored several strategies manufacturers employ to extend marketing exclusivity. The panel was moderated by Jan Berger, MD, MJ.

Speeding access to generic medications is a pillar of pharmacy benefit management, as well as a key systematic way of managing pharmaceutical cost trends. The small-molecule blockbuster medications have in recent years entered a "patent cliff," wherein a significant number of generic drugs has begun to enter the marketplace. This wave has increased competition and yielded significant cost savings for a number of stakeholders. Several important small-molecule drugs have US patent expirations slated for 2016, including Benicar (olmesartan medoxomil), Benicar HCT (olmesartan medoxomil and hydrochlorothiazide), Crestor (rosuvastatin calcium), Cubicin (daptomycin), Zetia (ezetimibe),[1] and perhaps, although unlikely, Zytiga (abiraterone acetate), as will be discussed later in this article. Health plans, insurers, and pharmacy benefit managers (PBMs) add generics to their drug formularies as quickly as possible to benefit from savings versus comparator branded medications.

When developing a medicine to bring to the market, a pharmaceutical company may spend up to $2.6 billion (in 2013 US dollars)[2] to identify a compound and complete the necessary preclinical and clinical trials to file a new drug application (NDA) with the FDA. This investment results in precious intellectual property that can bring in revenue for a drug maker for years to come. Without protection of this intellectual property, the pharmaceutical industry would be reluctant to invest the capital needed to develop innovative new products to improve health for individual patients and populations.

In recent years, an increased amount of attention has been paid to pharmaceutical patents and litigation in the press and with payers.[3] With the increased attention on pharmaceutical patents, there

ABSTRACT

Drug manufacturers may employ various life-cycle management patent strategies, which may impact managed care decision making regarding formulary planning and management strategies when single-source, branded oral pharmaceutical products move to generic status. Passage of the Hatch-Waxman Act enabled more rapid access to generic medications through the abbreviated new drug application process. Patent expirations of small-molecule medications and approvals of generic versions have led to substantial cost savings for health plans, government programs, insurers, pharmacy benefits managers, and their customers. However, considering that the cost of developing a single medication is estimated at $2.6 billion (2013 dollars), pharmaceutical patent protection enables companies to recoup investments, creating an incentive for innovation. Under current law, patent protection holds for 20 years from time of patent filing, although much of this time is spent in product development and regulatory review, leaving an effective remaining patent life of 7 to 10 years at the time of approval. To extend the product life cycle, drug manufacturers may develop variations of originator products and file for patents on isomers, metabolites, prodrugs, new drug formulations (eg, extended-release versions), and fixed-dose combinations. These additional patents and the complexities surrounding the timing of generic availability create challenges for managed care stakeholders attempting to gauge when generics may enter the market. An understanding of pharmaceutical patents and how intellectual property protection may be extended would benefit managed care stakeholders and help inform decisions regarding benefit management.

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For author information and disclosures, see end of text.

is a need for better understanding of the relationship between patents and exclusivity, along with the balance between protecting innovation and promoting access to less costly medications. These factors affect pharmaceutical life-cycle management, the transition of products from single-source to multisource status, as well as formulary decision making and pharmacy budget planning.

The Patent System

Pharmaceutical intellectual property is protected primarily through the US patent system. In the most basic case, a pharmaceutical patent is sought for the creation of a new molecular entity (a "composition-of-matter" patent). The manufacturer applies to the US Patent and Trademark Office (USPTO), which reviews the patent application and makes a decision regarding approval or rejection.[4] Patents can be filed to protect, not only the molecule itself, but the process used to manufacture the drug, how the drug is used, and new formulations of the drug.

All patents on branded pharmaceutical products are registered and listed in an addendum to the FDA-published *Orange Book*.[5] In most cases, the patent is issued by the USPTO an average of 3.4 years after filing for a conventional drug and 4.4 years after filing for a biologic.[6]

According to statute, the granting of a pharmaceutical patent includes protection on that patent for a period of 20 years from time of patent filing. Patent protection may be extended beyond 20 years, depending on whether the processing and review of the patent application was delayed at the patent office or delays were incurred during product review by the FDA.[7]

During the 20-year life of the patent, other drug manufacturers may not sell generic alternatives of the product without the risk of lawsuit and substantial court-approved penalties. In practice, much of the initial 20 years of exclusivity may be spent in product development and regulatory review. The remaining years of patent protection, and the market exclusivity that results, provide economic incentives and considerable potential revenue for a drug company, revenue that is critical to its ability to recover the capital it invests in research and development (R&D) and turn a profit. Most companies also reinvest a substantial portion of revenue back into R&D, so revenue is essential to the development of future drug therapies. The results of a survey by the Pharmaceutical Research and Manufacturers of America indicated that member companies spent 18.6% of total sales on R&D in 2014.[8]

Product Patents Versus Marketing Exclusivity

Patents and exclusivity work in a similar fashion, but are different from one another. Marketing exclusivity interacts to some extent with patent laws. It is granted through regulatory action by the FDA and guided by statute (the Federal Food, Drug, and Cosmetic Act and the Hatch-Waxman Act). Exclusive marketing rights are granted by the FDA upon approval of a drug, and this period of marketing exclusivity may or may not run concurrently with the period of patent protection.

In its essence, regulatory exclusivity is a congressionally mandated monopoly under the law. It allows a brand name manufacturer a certain guaranteed period of protection, regardless of what patents they may or may not have. The protection provided by patents, however, is not guaranteed, as discussed later.

Before passage of the Hatch-Waxman Act in 1984 (also known as the Drug Price Competition and Patent Term Restoration Act of 1984 [Public Law 98-417]), the US patent system was the sole protector of intellectual property. Marketing exclusivity was granted to the patent holder, but a finite period after which marketing exclusivity would expire was not defined. Manufacturers who were interested in developing generic drugs had to face the same battery of clinical testing required by the FDA of manufacturers of new chemical entities.[7]

For manufacturers of branded drugs, one problem with the system before 1984 was that the patents could be found to be invalid or unenforceable. Marketing or regulatory exclusivity may be a stronger shield to protect intellectual property. However, legislative and regulatory efforts have not been used solely to protect intellectual property; generally, the intention of these statutes has been to balance patent protection with beneficial access to high-quality, affordable medicines (ie, generics), with the additional result being a period of market exclusivity.

Hatch-Waxman Act Basics

The Hatch-Waxman Act of 1984 sought to speed access to generic medications by providing generic manufacturers with incentives and a pathway for approval. Hatch-Waxman also provided innovators with meaningful patent protection and an opportunity to recoup their investment, and also provided incentives to generic manufacturers to promote the rapid availability of generic alternatives.[9]

The Act established regulatory exclusivity periods for branded and first generic agents. Exclusivity periods were included in the Act as a lever to promote a balance between new drug innovation and generic drug competition. For example, the first generic manufacturer to challenge a patent for a branded product listed in the *Orange Book* is awarded a 180-day exclusivity period, beginning at FDA approval.[7]

One of the main objectives of the Hatch-Waxman legislation was to promulgate a formal pathway for the introduction of generic drugs, in an effort to bring generics to the market sooner. To achieve this, the Act introduced the abbreviated new drug application (ANDA) process, and detailed the studies and data required by the FDA to evaluate a generic drug for approval.[7]

Under Hatch-Waxman, upon approval of a new chemical entity, the FDA grants a regulatory exclusivity period of 5 years (regardless of patent life remaining). Importantly, as some agents take a longer time to obtain FDA approval, the Hatch-Waxman

Act provides patent-term extensions for those products where a longer time is required by the FDA to review the drug application.[7]

Patents can be filed and granted by the USPTO anywhere along the development life cycle of a drug. Some patent approvals may indirectly extend market exclusivity of a product.

The *Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations)*[5] is published by the FDA. It lists prescription drug products and over-the-counter agents that are approved by the FDA as safe and effective. Manufacturers of branded products must identify USPTO-approved relevant patents and provide information on them, including patent expiration dates, to the FDA, which then publishes this information in the *Orange Book*.

Generic Drug Approval, Patents, and Exclusivity

A generic manufacturer can bring their drug to market in 2 ways: (1) it can file for approval, and if approved, launch after the branded product's patents and exclusivity period expire, or (2) it can challenge the validity of the branded manufacturer's patent. The latter usually occurs through the litigation process.

The process for challenging a patent listed in the *Orange Book* generally occurs in the following steps:

1. The generic manufacturer submits an ANDA application to the FDA (including their certifying non-infringement of originator's patents).
2. A notice letter is sent to the patent holder. When a generic manufacturer files an ANDA, the patent holder may consider this as an act of infringement, and can file suit for patent infringement.
3. If the patent holder sues the generic manufacturer within 45 days of the receipt of the notice letter, the FDA may not grant final approval of the generic application for 30 months from the time of loss of regulatory exclusivity, unless a district court rules for the generic drug manufacturer before then, allowing time for the patent challenge to be decided in court.
4. If the patent ruling is in favor of the generic-drug manufacturer, the patent holder may appeal the loss of the generic manufacturer's challenge. In this case, the appeals process takes an average of roughly 14 months.[10] During the appeals process, the generic drug maker may consider launching the generic drug "at risk," meaning before litigation has been resolved. However, if the patent holder wins the appeal, the patent holder can seek monetary damages for the revenues lost. Therefore, launching at risk can carry significant financial implications, especially in the case of a generic for a blockbuster medication. In practical terms, between the initial hearing process and potential appeal process, the patent holder may achieve up to an additional 30 to 45 months of effective exclusivity, beyond the point of loss of regulatory exclusivity.

The generic manufacturer's objective in challenging an existing patent is to initiate the patent-infringement evaluation process to coincide with the FDA's review of the drug application. In the best-case scenario, the FDA's review will be completed around the same time as the patent infringement case is decided, allowing the drug to be marketed as soon as possible thereafter.

SIDEBAR: The Relative Strengths of Patents

Although patents may seem to be an impregnable barrier to early generic competition, this is not necessarily the case. Certain types of patents are stronger than others. "Patents are never a sure thing. There is no perfect patent, I imagine," said roundtable participant Kurt Karst. "Patents can be found to be invalid or unenforceable, or perhaps even not infringed by a generic drug manufacturer."

Part of the reason relates to an imperfect system of reviewing and approving patents. Often, litigation contesting the validity of a patent involves materials or source information that the patent office didn't possess at the time of the initial patent approval or that was not fully understood by the reviewers.

In that context, new composition-of-matter patents seem to offer the strongest protection; they are the most difficult for generic drug manufacturers to challenge in court, according to the patent experts on the roundtable.

In contrast, method-of-use and formulation patents, which can include new routes of administration and unique drug delivery devices, may offer less protection. The reason for this vulnerability is that generic manufacturers can often utilize other mechanisms for drug delivery or develop new ways to bind molecules for oral or intravenous use.

Likewise, method-of-manufacturing patents may also offer less protection than a composition-of-matter patent. For example, drug makers may produce a bioequivalent product by manufacturing with different excipients or with other established methods.

Extending the Product Life Cycle and Protecting Product Revenue

As indicated earlier, the patent life remaining on a product at time of approval may be only 7 to 10 years. The complexities of mar-

ket exclusivity and patent litigation frustrate payers, physicians, patient groups, and other stakeholders. As there is no certainty as to the timing of availability of generics, these stakeholders cannot formulate a plan for the introduction of a generic version of a specific product. For example, uncertainty around patent expiration and generic product introduction makes pharmacy benefit planning (budgeting/formulary) more difficult.

SIDEBAR: Payer Perspective on Brand Extension

Payers are frustrated by the extension of branded product life cycles through the granting of patents on isomers, metabolites, prodrugs, new delivery methods, and fixed-dose combinations; some of these modifications may improve aspects of drug effectiveness, safety, or adherence, while others may not.

Extending the life cycle of a brand is extremely profitable to the manufacturer of a product nearing the end of its patent life. "With a blockbuster drug, there's a lot to be gained by even a bit of an extension of that brand," said Peggy Johnson, RPh. If a branded drug's revenue averages $1 billion per year, it has paid off the bulk of the research and development costs, and marketing and sales overhead years ago, to the point that perhaps 90% of its revenue in its final years of exclusivity is profit. This profit may be used to fund future research and development. Margins of this magnitude not only compel the efforts made to extend the life cycle as long as possible, but also greatly increases the amount a generic manufacturer who launches at risk, before patent litigation is complete, may have to compensate the branded manufacturer.

Another way manufacturers can extend revenues from their brand is to produce its own generic version of the drug; it markets its generic version as an "authorized generic." The FDA lists 980 authorized generics (although these include multiple dosages and forms of individual drugs), from Accupril (quinapril hydrochloride) to Zyvox (linezolid).[11]

Improving and Expanding a Drug's Utility

Manufacturers often conduct additional research in an effort to enhance their marketed agents. Product enhancements may improve the drug's utility in clinical care, extend patent protection, and increase revenues. The result of the research may be new uses and new indications. Many times, drug companies evaluate new routes of administration for their product (injectable, sublingual, intranasal, etc), which may increase absorption or enhance adherence.[4] For certain drugs, like asthma inhalers or insulin pens, this may be in the form of "improved" delivery devices customized for that drug.[12]

Commonly, manufacturers file patents on new drug formulations (eg, extended-release versions) or formulations that contain different excipients (to help stabilize the active ingredient, for instance). Furthermore, manufacturers may patent a new manufacturing process, which helps create greater quantities of medication more efficiently or with fewer inactive ingredients. As previously discussed, these improvements may not effectively shield the product from patent challenges.

The combination of the existing product with a new or other marketed agent is another way to extend the life cycle of a drug. This is the case with several diabetes agents (eg, combinations with metformin).

SIDEBAR: Price Increases on Products Nearing Patent Expiration

Price increases toward the end of patent life are also a mechanism for maintaining revenue.[13] Payers object, as these increases have little to do with value of the product; rather, the increases are attempts to maximize revenue just before patent expiration. Dr Dunn said, "Historically, we have seen significant price increases in the 6 to 12 to 18 months leading up to a patent loss. There's nothing we can do about that. We're probably not going to take a drug off formulary and reinstate it 6 months later. But that's why we push so hard for price protection."

Ms Johnson added that price increases often go beyond the patent expiration to maximize revenue for the branded manufacturer. She stated, "Price protection rebates have been negotiated in part to address this scenario," not only for the originator product, but for other brands in the class. A new generic entering a drug category threatens "not just the drug that's going to lose its patent. Every brand name drug in that class feels their market share will be threatened because the class is going to be disrupted. So other drug makers in the class may raise their prices as well," Ms Johnson explained.

This leads, according to the payers, to the perception that the branded pharmaceutical companies will charge "pretty much whatever the market will bear," and to the skepticism of payers that many actions taken by pharmaceutical companies to improve existing products are more product-line extensions than actual product enhancements.

Payers and the Transition From Branded to Generic

Health plans, insurers, and PBMs monitor the anticipated patent expiration dates for high-cost agents, but as indicated earlier, their confidence level of exactly when a generic will be introduced is fairly low. Any anticipated price increases within 6 to 18 months prior to patent loss are discussed during pharmacy budget planning and P&T committee meetings.

SIDEBAR: Payer Perspective on Planning for the Introduction of Generics

Ms Johnson emphasized that "plans have become pretty good at what we call managing the pipeline of generic opportunity."

The pharmacy executives noted that payers often start considering the potential effects of generics to these blockbusters 18 to 24 months ahead of time, especially if the P&T committee reviews a class once annually.

Although payers don't actively manage their business around patents, per se, this can definitely be part of the planning process for blockbuster brands (eg, Lipitor [atorvastatin calcium], Prilosec [omeprazole], Nexium [esomeprazole], Crestor [rosuvastatin calcium], Abilify [aripiprazole]).

Dr Dunn agreed, adding that "Payers spend a good deal of time with actuaries and underwriters, trying to anticipate rebate and revenue changes, particularly for drugs in high-cost or high-utilization categories. We take a long-term approach to this. We're probably not going to move drugs back and forth in anticipation of a patent loss."

The near-term entry of a generic drug can also have implications for other medications in the same class. This can open negotiations for expiring contracts on branded agents. Payers seek to determine which of several products in a therapeutic class may be first to go off-patent. This consideration may influence future plans, as can the first generic launch within a therapeutic class, which could have implications in P&T committee discussions—beyond the innovator product to other similar drugs. For example, if the category comprises therapeutically equivalent products, these other products may be subject to a step through the new generic.

In some cases, an impending generic entry into a drug class will have a very different impact, according to Dr Dunn: "If we do know a major brand is going off-patent in 6 months, for example, and another branded drug is entering the category, we're much less likely to add that new brand drug to the formulary, because we don't want to take market share away from the brand that's going off-patent." This tactic would enable the payer to save more money on a larger segment of the total patient population, by promoting the conversion of a higher volume of prescriptions within a class to the new generic medication by limiting competition from a "new and improved" brand entity.

SIDEBAR: Formulary Placement of Recently Approved Generics

Many P&T committees do address financial and budgeting questions, particularly in discussions of cost-effectiveness or value-based benefits. In most cases, an initial generic drug introduction does not usually require a P&T committee meeting for formulary inclusion. Discussions by the P&T committee involve comparative efficacy, safety, and then cost. Since the FDA has approved the agent, presumably as bioequivalent to the original brand, the first 2 issues are moot. Few or no head-to-head studies exist between "improved" brands and new generics to inform the value discussion, so payers often resort to cost discussions in these cases. In most cases, the new generic is offered at a significant discount to the branded product.

Ms Johnson remarked that when a generic is approved, generally, the new generic is automatically placed on the formulary (tier 1), and the innovator brand is usually

moved to nonpreferred status or excluded from the formulary (the latter in the case of a 2-tier or closed formulary). "It doesn't generally impact tier positioning for the rest of the category, because we've already put a lot of time into crafting that strategy around cost-effectiveness and value." However, she pointed out, other brands in the category may now be subject to step therapy with the new generic entity. Later, when more than one generic product becomes available in a class, a tipping point may be reached such that all brand products are relegated to nonpreferred or nonformulary status.

In certain situations, if the generic is not priced at a significant discount, it may be placed in a higher tier, solely based on cost (nonpreferred generic tier or a tier developed for brand name products). Tier designations may be related more to underlying drug cost rather than brand/generic classification.

Case Studies

During the second part of the roundtable, the moderator asked participants to comment on several case studies involving specific products, to gain feedback and perspective from the payers and attorneys regarding the particular circumstances surrounding the introduction of generic versions.

Case Study 1: Gleevec (imatinib)

Gleevec (imatinib) is indicated for the treatment of chronic myelogenous leukemia (CML). Novartis' composition-of-matter patent for Gleevec expired in January 2016, and the first generic version of imatinib was marketed in the United States in February 2016 by Sun Pharmaceuticals.[14]

SIDEBAR: Payer Perspectives on the Introduction of Generic Imatinib

The introduction of a generic version of imatinib was followed closely by payer pharmacy directors, said Dr Dunn. "It is really a precedent setter for what we do in the oral oncology space. However, we didn't change anything in anticipation of its launch, because the brand was not disadvantaged. We are now covering the generic and not covering the brand. It will shape anything that occurs in the future with this class of tyrosine-kinase inhibitors."

"A patent litigation challenge added uncertainty to the timeline and ultimately delayed the generic launch for 7 months," added Ms Johnson. "Novartis initiated discussions about extending brand contracting in light of an authorized generic launch and also offered patient copay discounts in order to compete with the generic product."

Dr Dunn's organization placed the generic on formulary immediately "because it didn't affect contracts. It is on a specialty tier rather than the traditional generic tier, however. The brand was removed from formulary at the next P&T committee meeting. Today, other tyrosine-kinase inhibitor brands are stepped through the generic for the labeled indications via the prior authorization process."

The short-term budget impact of this generic may be less than pharmacy directors anticipated, Dr Dunn pointed out, because the generic is not priced substantially less than the brand. However, its budget impact may grow over time, particularly with the expiration of the 180-day exclusivity period and the influx of additional generic competition. In addition, the ability to step other tyrosine-kinase inhibitors for CML through the generic for new patients should generate further cost savings.

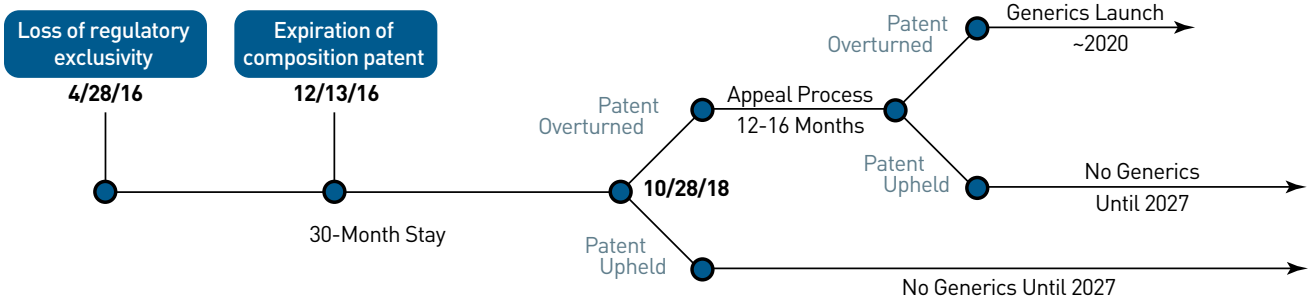
Case Study 2: Zytiga (abiraterone acetate)

The FDA approved Zytiga (abiraterone acetate) for use in combination with prednisone for the treatment of men with metastatic castration-resistant prostate cancer who have received prior chemotherapy in April 2011.[15] A supplemental indication for use in men prior to receiving chemotherapy followed in December 2012.[16]

Three years after the initial approval of branded Zytiga (abiraterone acetate), the manufacturer of Zytiga received approval for an additional patent, which will extend the period of exclusivity beyond that of the composition-of-matter patent. This new intellectual property protection was a "method-of-use" patent, which covered the coadministration of prednisone (given as a separate pill) with Zytiga, a dosing regimen that was already prescribed in the FDA-approved product label. This patent was listed in the *Orange Book* and provides patent protection for Zytiga potentially well into 2027—more than 10 years beyond the expiration of the Zytiga molecule patient in late 2016.

The **Figure** shows the timeline of activity leading to the potential launch of a generic for Zytiga. The original 5 years of FDA regulatory exclusivity for Zytiga as a new chemical entity expired on April 28, 2016, and the composition-of-matter patent will expire on December

FIGURE. Zytiga Exclusivity Decision Tree



13, 2016. The 30-month stay on FDA approval for any generic expires in late October 2018, and should the manufacturer lose the patent case being subject to litigation brought by generic manufacturers to challenge the new dosing patent and choose to appeal the ruling, the appeals process may last a further 12 to 16 months, until the end of 2019. This would mean that the earliest a generic might reach the market is early 2020. Should the manufacturer win the dosing patent challenge by the generic manufacturers (or lose the challenge, but go on to win the appeal), the addition of the new dosing patent would extend patent protection for Zytiga into 2027.

SIDEBAR: Panelist Perspectives on Zytiga Patent Protection

According to W. Chad Shear, "Arguably, the additional patents offer an additional exclusivity for 20 years from their date of filing. However, those patents are subject to challenge by would-be generics, and are in fact being challenged right now in District Court and at the USPTO."

The additional patent for Zytiga (patent 8,822,438) is listed in the FDA's *Orange Book*. "Companies filing applications to market generic Zytiga will be required to certify to FDA that they do not infringe the dosing regimen patent," added Kurt Karst. "This recently issued dosing regimen patent listing is therefore a barrier to generic competition, unless a court ultimately denies the patent as invalid and/or noninfringed."

Health plans and formulary managers, though generally unaware of patent extension efforts or patent litigation status, do monitor the timing of potential generic availability of key products, as it is relatively easy to track the expiry of regulatory exclusivity of branded products on the FDA website, and ANDA applications by generic companies trigger patent litigation, on which information is publicly available.

Ms Johnson stated, "I personally was not aware of the patent extension and potential for a dosing regimen patent related to the coadministration of prednisone. This is a fairly crowded category, so value (outcomes) will be a consideration relative to formulary placement." She continued, "Contracts are generally not long term (more than 1-2 years) and generally have clauses related to market changes/new market entrants. Brand competition is a factor here, as well as patent extension."

Case Study 3: Namenda (memantine hydrochloride)/ Namenda XR (memantine hydrochloride, extended release)

A "product hop" is the substitution—not addition—of a new branded formulation of a prescription drug for an old version by a manufacturer, with the intention of forestalling generic competition. Multiple examples of product hops have been seen over the years. For this case study, the focus was on an extended-release, once-daily dosage form of memantine (called Namenda XR), which was introduced by Forest Laboratories (now Allergan).[17] The manufacturer soon attempted to take away patient access to the immediate-release product, which was dosed twice daily.[18]

Furthermore, in a product hop example, the original formulation's clinical effect is unaltered, but the medication is now somewhat different. In other words, the new version will not be considered AB-rated for substitution purposes. The sole beneficiary is the drug maker, who may avoid generic substitution and may reinforce its revenue stream.[19]

SIDEBAR: Payer Perspectives on the "Product Hop"

Unless there are clear benefits, payers are wary of the introduction of extended-release versions. "Generally, I would say these are not clinical issues. The perception is not very good from a payer perspective," remarked Dr Dunn, "unless there are very explicit adherence issues [with the original drug] that will lead to obvious benefits [with the extended-release version]. We would treat any of these agents like a new brand. We don't generally jump on board with these sustained-release or extended-release agents."

Product hops tend to elicit more visceral reactions from payers, because they are associated with higher costs, with no additional clinical benefits. Ms Johnson noted that "the manufacturer's attempt to take the immediate-release version off the market after introducing the XR version 'didn't work'. These product hops are not viewed as clinical differentiators or value drivers. We treat the extended-release products like other brands, and it's much less likely they're going to be positioned as preferred agents."

Ms Johnson also emphasized that removal of the previous version prevented the validation of the new product's value compared with the original product, making it more difficult to determine appropriate formulary positioning for the new product.

"This is really an egregious use of the patent extension, and it created a payer backlash," commented Ms Johnson, because Forest sent the message that "it either doesn't have faith in the original product, or that it simply wanted to move all of the Namenda business to the more expensive brand."

The Namenda versus Namenda XR product hop landed in the court system, as the State of New York brought suit against Actavis (which purchased Forest, before being acquired itself by Allergan). A decision on May 22, 2015 by the US Court of Appeals for the Second Circuit agreed with a lower court ruling, stating that the "Defendants' hard switch would likely have anticompetitive and exclusionary effects on competition in the memantine market, creating a 'dangerous probability' that Defendants would maintain their monopoly power after generics enter the market."[20]

Conclusion

Pathways for the protection of pharmaceutical intellectual property are complex. The Hatch-Waxman Act of 1984 defined the pathway for generic drug approvals but also set patent and market exclusivities for different drug marketing scenarios. These protection pathways have evolved since that time, influenced by changes in legislation and the regulatory environment.

The Act's system for patent protection and generic drug approval offers opportunities to not only guard intellectual property, but also to encourage innovation, including improvements to the drug in question. However, not all new pharmaceutical patents result in true innovation or in improvement in patient care, and payers are often skeptical of claims made around such product refinements.

Managed care stakeholders should have an understanding of pharmaceutical patents and ways in which intellectual property can be leveraged or extended, as this information can help clarify the availability of therapeutic alternatives, such as generics and the timing of their launches. With regard to blockbuster brands going off-patent, understanding this information can assist payers in budget planning, contract negotiation, and even P&T committee decision making.

An understanding of the patent system can also help improve payers' appreciation of new product launches—for example, whether an approved product is a new molecular entity or simply a new formulation. This information can affect formulary positioning as well as patient care.

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REFERENCES

1. Song CH, Han JW. Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry. *Springerplus*. 2016;5(1):692-706. doi: 10.1186/s40064-016-2323-1.

2. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ*. 2016;47:20-33. doi: 10.1016/j.jhealeco.2016.01.012.

3. Potter A. Interpreting the BPCIA—is the "patent dance" mandatory? *The Columbia Science and*

Technology Law Review website. http://stlr.org/2015/03/31/interpreting-the-bpcia-is-the-patent-dance-mandatory. Published March 31, 2015. Accessed August 16, 2016.

4. Gupta H, Kumar S, Roy SK, Gaud RS. Patent protection strategies. *J Pharm Bioallied Sci*. 2010;2(1):2-7. doi: 10.4103/0975-7406.62694.

5. U.S. Department Of Health And Human Services. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*. 36th ed. Silver Spring, MD: U.S. Food and Drug Administration; 2016. www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/ucm071436.pdf. Accessed April 27, 2016.

6. Fernandez DS, Huie JT. Strategic balancing of patent and FDA approval processes to maximize market exclusivity. IP Loft website. www.iploft.com/PTO-FDA.pdf. Accessed April 28, 2016.

7. Pensabene LB, Gregory D. Hatch-Waxman Act: overview. *Practical Law* website. http://us.practicallaw.com/9-523-2397. Accessed August 16, 2016.

8. Pharmaceutical Research and Manufacturers of America. 2016 PhRMA Annual Membership Survey. Pharmaceutical Research and Manufacturers of America website. www.phrma.org/sites/default/files/pdf/annual-membership-survey-results.pdf. Published 2016. Accessed September 27, 2016.

9. Troy DE. Drug Price Competition and Patent Restoration Act of 1984 (Hatch-Waxman amendments). FDA website. www.fda.gov/newsevents/testimony/ucm115033.htm. Published August 1, 2003. Accessed April 28, 2016.

10. Hungar TG, Sitzman M. Federal circuit year in review 2013/2014: intellectual property and appellate practice groups. Gibson, Dunn & Crutcher LLP website. www.gibsondunn.com/publications/Documents/Federal-Circuit-2013-2014-Year-in-Review.pdf. Published 2015. Accessed September 8, 2016.

11. FDA listing of authorized generics as of June 29, 2016. FDA website. www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM183605.pdf. Accessed August 12, 2016.

12. Beall RF, Nickerson JW, Kaplan WA, Attaran A. Is patent "evergreening" restricting access to medicine/device combination products? *PloS One*. 2016;11(2):e0148939. doi: 10.1371/journal.pone.0148939.

13. Staton T. 10 Big brands keep pumping out big bucks, with a little help from price hikes. *FiercePharma* website. www.fiercepharma.com/sales-and-marketing/10-big-brands-keep-pumping-out-big-bucks-a-little-help-from-price-hikes. Published May 7, 2014. Accessed August 16, 2016.

14. Conti RM, Padula WV, Larson RA. Changing the cost of care for chronic myeloid leukemia: the availability of generic imatinib in the USA and the EU. *Ann Hematol*. 2015;94(suppl 2):S249-S257. doi: 10.1007/s00277-015-2319-x.

15. BTG plc: ZYTIGA™ (abiraterone acetate) approved in the US [press release]. London, UK: BTG International Ltd; May 3, 2011. www.btgplc.com/media/press-releases/btg-plc-zytiga-abiraterone-acetate-approved-in-the-us/. Accessed September 14, 2016.

16. NDA 202379/S-005 supplement approval (Zytiga). FDA website. www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202379Orig1s005ltr.pdf. Accessed September 27, 2016.

17. Drug approval package: Namenda XR (memantine hydrochloride) 7 mg, 14 mg, 21 mg, & 28 mg extended release capsules. FDA website. www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525s000_namenda_xr_toc.cfm. Published June 21, 2010. Accessed August 20, 2016.

18. Klusty T. A legal test for the pharmacy company practice of "product hopping." *AMA J Ethics*. 2015;17(8):760-762. doi: 10.1001/journalofethics.2015.17.8.hlaw2-1508.

19. Lukens JT. Pharmaceutical product hop antitrust case reaches third circuit. Faruqi & Faruqi, LLP website. www.faruqilaw.net/blog/id/174/pharmaceutical-product-hop-antitrust-case-reaches-third-circuit. Published June 2, 2016. Accessed August 20, 2016.

20. In the United States Court of Appeals for the Second Circuit: State of New York v. Actavis. Opinion No. 14-4624. Filed under seal May 22, 2015. ■

NOTES

EXHIBIT T

FDA Approves Pre-Chemo Enzalutamide for mCRPC

Silas Inman @silasinman
Published: Wednesday, Sep 10, 2014


Tomasz M. Beer, MD

The FDA has expanded the approval for enzalutamide (Xtandi) to include the treatment of men with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC), based on survival data from the phase III PREVAIL trial.

In the study, treatment with enzalutamide improved overall survival (OS) by 29% and radiographic progression-free survival (rPFS) by 81% compared with placebo. The expanded indication for the androgen receptor inhibitor was granted under the FDA's priority review program. Enzalutamide was initially approved for chemotherapy-pretreated men with mCRPC in August 2012.

"Enzalutamide has been shown to extend overall survival and significantly delay the progression of prostate cancer," co-principal investigator Tomasz M. Beer, MD, the deputy director of the Knight Cancer Institute and professor of medicine at Oregon Health & Science University, said in a press release. "In the PREVAIL trial, the median time to initiating chemotherapy was delayed by 17 months with enzalutamide treatment as compared to placebo, so the result is a meaningful period of time during which men have their disease controlled without the need for chemotherapy."

In the phase III study, 1717 men with a median age of 71 years received treatment with enzalutamide (n = 872) or placebo (n = 845). Enzalutamide was administered at 160 mg daily. Concurrent glucocorticoids were administered to 27% of patients treated with enzalutamide and 30% of patients in the placebo arm.Â The co-primary endpoints of the study were OS and rPFS. Castration-resistance was determined by PSA-only progression in 43% of patients and 54% demonstrated radiographic evidence of disease progression prior to entering the study.Â
Â
An interim analysis was conducted following 540 deaths, which demonstrated a statistically significant advantage for enzalutamide for both OS and rPFS. At this point, the study was halted and men in the placebo arm were allowed to crossover to receive enzalutamide.

The most common subsequent therapies for patients in the enzalutamide and placebo arm were docetaxel (33% and 57%) and abiraterone acetate (21% and 46%). Forty percent of patients in the enzalutamide arm received subsequent therapies compared with 70% with placebo.

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According to data published in *The New England Journal of Medicine*, the median OS was 32.4 months with enzalutamide versus 30.2 months with placebo (HR = 0.71; *P* <.0001). The median rPFS was not yet reached in the enzalutamide arm compared with 3.9 months with placebo (HR = 0.19; *P* <.0001). The overall response rate was 58.8% versus 5%, for enzalutamide and placebo, respectively (*P* <.0001).

The median time to the initiation of chemotherapy was prolonged by 17.2 months for enzalutamide compared with placebo (28 vs 10.8 months; HR = 0.35; *P* < .0001). The median time to first skeletal-related event was 31.1 months for enzalutamide and 31.3 months with placebo (HR = 0.72; *P* <.0001). A PSA decline of greater than 90% was detected in 46.8% of patients treated with enzalutamide compared with 1.2% for placebo (*P* <.0001).

The most common adverse events for enzalutamide versus placebo were fatigue (35.6% vs 25.8%), back pain (27.0% vs 22.2%), constipation (22.2% vs 17.2%), and arthralgia (20.3% vs 16.0%). Seizure was reported in 1 patient in each treatment arm (0.1%). Patients with a prior history of seizure were excluded from the study.

Grade 3/4 adverse events were reported in 43% of the patients in the enzalutamide arm compared with 37% with placebo. The median time to the first grade 3/4 event was 22.3 months with enzalutamide versus 13.3 months with placebo.

“By and large Xtandi was well tolerated. In the PREVAIL trial, the side effects that we observed more commonly with Xtandi than with placebo were fatigue, back pain, joint pains, constipation, hot flushes, hypertension, upper respiratory tract infection, and falls," Beer said in an interview. "We saw one seizure event in the Xtandi group and one in the placebo group.”

Medivation, Inc., and Astellas Pharma, Inc., co-develop enzalutamide. The expansion of the label triggered a $90 million payment by Astellas to Medivation under an agreement between the two companies.

"The FDA's priority review and approval of this new indication for Xtandi now enables the use of an important therapy by patients with metastatic castration-resistant prostate cancer at all stages of their disease," said Sef Kurstjens, MD, PhD, chief medical officer of Astellas Pharma Inc. and president of Astellas Pharma Global Development, Inc. "We are pleased that these patients now have Xtandi available as a treatment option."

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EXHIBIT U

FDA APPROVALS **PERSPECTIVE**

FDA approves enzalutamide for metastatic castration-resistant prostate cancer

HemOnc Today, September 25, 2012

The FDA today approved enzalutamide for patients with metastatic castration-resistant prostate cancer that has spread or recurred, despite medical or surgical therapy to reduce testosterone.

Approved for prostate cancer patients previously treated with docetaxel, enzalutamide (Xtandi, Medivation Inc.) was reviewed under the FDA's priority review program.

"The need for additional treatment options for advanced prostate cancer continues to be important for patients," **Richard Pazdur, MD**, director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research said in an FDA release. "Xtandi is the latest treatment for this disease to demonstrate its ability to extend a patient's life."

The FDA based its approval on a study of 1,199 patients with metastatic castration-resistant prostate cancer who had received prior treatment with docetaxel. The study was defined to measure OS in men receiving enzalutamide compared with men receiving placebo. The median OS for patients receiving enzalutamide was 18.4 months vs. 13.6 months for the patients who received placebo.

The most commonly observed adverse effects in study participants assigned enzalutamide were weakness or fatigue; hematuria; spinal cord compression and cauda equina syndrome; tissue swelling; diarrhea; musculoskeletal pain; headache; respiratory infections; dizziness; difficulty sleeping; tingling sensations; anxiety; and elevated blood pressure.

Seizures were reported in approximately 1% of those patients who received enzalutamide, at which point therapy was discontinued.

Exclusion criteria for the study consisted of patients with a history of seizure, temporary decrease in blood to the brain during the previous 12 months, reported underlying brain injury with notable loss of consciousness, stroke, brain metastases

and patients taking medications that could lower the seizure threshold. At present, the safety profile for enzalutamide is unknown in patients with these conditions.

PERSPECTIVE

FDA approval of enzalutamide is another step in the recent substantial progress in defining new therapies for prostate cancer. It is of interest – and sobering – that enzalutamide and abiraterone are the first agents whose mechanisms of action are unique in modulating the influences of androgen on prostate cancer, since the approval of flutamide (non-steroidal antiandrogen) and goserelin (LHRH analogue) in 1989. Enzalutamide interacts with the androgen receptor, but its mechanisms of action are distinct from other androgen receptor interactive agents in that enzalutamide inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment.

As should be the case with any important discovery in basic, translational or clinical research, the approval of enzalutamide sets the stage for the study of this agent in situations other than prostate cancer progressive despite castration. The efficacy and toxicity of this agent needs to be compared to abiraterone in docetaxel-refractory patients and studied in less advanced situations and in combination with LHRH analogues and/or abiraterone, in order to determine the full spectrum of activity –and importantly, toxicity of ablation of androgen signaling in treating men with prostate cancer. As the cost of all the newly approved agents is very high, delineation of the most cost-effective approaches to their use are also important. Some of these studies are underway and one hopes these questions can be answered sooner rather than later.

Donald L. Trump, MD, FACP

HemOnc Today Editorial Board member

EXHIBIT V

Cancer Treatment Reviews 40 (2014) 170–177

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New Drugs

Second-line treatment options in metastatic castration-resistant prostate cancer: A comparison of key trials with recently approved agents

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SUMMARY

Standard first-line treatment for metastatic castration-resistant prostate cancer (mCRPC) is docetaxel plus prednisone; however, patients will usually experience disease progression during or after docetaxel treatment due to inherent or acquired resistance. Before 2010, second-line options for mCRPC were limited. However, cabazitaxel, abiraterone acetate and enzalutamide have since been approved for patients with mCRPC whose disease has progressed during or after receiving docetaxel, based on the Phase III trials TROPIC, COU-AA-301 and AFFIRM. In all three trials, an overall survival benefit (primary endpoint) was seen in the experimental arm compared with the control arm: 15.1 vs. 12.7 months for cabazitaxel plus prednisone compared with mitoxantrone plus prednisone in TROPIC (hazard ratio [HR] 0.70; $P < 0.0001$); 14.8 vs. 10.9 months for abiraterone acetateplus prednisone compared with placebo plus prednisone in COU-AA-301 (HR 0.65; $P < 0.001$); and 18.4 vs. 13.6 months for enzalutamide compared with placebo alone in AFFIRM (0.63; $P < 0.001$). However, differences in patient populations, comparators, and selection and/or definition of secondary endpoints make it difficult to draw direct cross-trial comparisons. Radium-223 dichloride has also been approved for patients with mCRPC with metastases to bone but not other organs. To date, no comparative trials or sequencing studies with newer agents have been performed. Without such data, treatment decisions must be based on evaluation of the existing evidence. This commentary compares and contrasts study designs and key data from each of these Phase III trials, and also discusses recent and ongoing clinical trials with new agents in the first- and second-line settings in mCRPC.

Introduction

Globally, prostate cancer is the second most frequently diagnosed cancer in men and is a major cause of mortality, representing 258,000 deaths in 2008 [1]. Although localized prostate cancer may be successfully treated with radiotherapy or surgery, many patients will develop metastatic disease [2–4]. Standard treatment for patients with metastatic prostate cancer is androgen-deprivation therapy; however, most patients will eventually develop resistance leading to disease progression (metastatic castration-resistant prostate cancer [mCRPC]). The introduction of highly effective novel therapies has resulted in increased overall survival (OS) in patients with mCRPC, from approximately 9–18 months [4] to >30 months in patients enrolled in recent clinical trials and expanded-access programs [5].

For patients with mCRPC, docetaxel (75 mg/m^2 every 3 weeks) was the first agent to demonstrate a survival benefit, and docetaxel plus prednisone (10 mg orally, daily) is the standard first-line therapy recommended by international guidelines for patients with symptomatic mCRPC who are suitable candidates for chemotherapy [2–4]. In randomized Phase III trials, docetaxel-based treatment showed a median OS benefit compared with mitoxantrone of 2–3 months, which was similar across subgroups (including both ⩽68 and ⩾69 years, both presence and absence of visceral

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metastases, and both low and highperformance status) [6]. In addition, prostate-specific antigen (PSA) response rates of 45–50%, an objective tumor response rate of 12–17% and an improvement in quality of life (QoL) compared with mitoxantrone were observed ($P < 0.01$) [6–8]. However, patients will usually experience disease progression either during or after receiving docetaxel regimens, due to resistance, either inherent or acquired through a number of different mechanisms [9,10]. In one study investigating a docetaxel-based regimen, the median time from first docetaxel dose to disease progression was 6.3 months [9].

Before 2010, second-line treatment options for mCRPC werelimited, with no benefits observed in terms of OS. Since 2010, however, three therapies have been approved for patients with mCRPC whose disease has progressed during or after receiving docetaxel: cabazitaxel, a novel tubulin-binding taxane (FDA approval in 2010; EMA approval in 2011) [11,12]; abiraterone acetate (AA), an oral androgen biosynthesis inhibitor (FDA and EMA approval in 2011) [13,14]; and enzalutamide, an oral androgen receptor antagonist (formerly known as MDV3100; FDA approval in 2012) [15]. Currently, cabazitaxel and AA are recommended in the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines as second-line options in this setting [2,4]. In addition, radium-223 dichloride, a novelalpha-emitting radiopharmaceutical agent that targets bone metastases owing to its chemical similarity to calcium, has recently been approved by the FDA for use in patients with mCRPC with symptomatic bone metastases and no known visceral metastatic disease. This agent demonstrated positive results compared with placebo in the Phase III ALSYMPCA trial in patients with mCRPC with bone metastases [16,17]. Based on the enrollment criteria for the ALSYMPCA study and efficacy data currently available, it is likely that radium-223 dichloride will be used both in patients with prior docetaxel therapy and in those who are not sufficiently fit to receive chemotherapy [16,17]. However, because this agent is not approved specifically in the second-line setting, it is not discussed in detail within this manuscript.

To date, no comparative trialsor sequencing studies with newer agents have been performed. In their absence, comparison of study designs and data from the pivotal Phase III trials can help to determine which agents are suitable for patients with different characteristics in second-line mCRPC. However, direct comparisons of studies are difficult when there are subtle differences in patient populations and in definitions of either treatment response or failure. This commentary compares and contrasts study designs and key data from each agent in patients with mCRPC whose disease has progressed during or following treatment with docetaxel.

Overview of Phase III trials of agents recently approved for second-line treatment of mCRPC

Cabazitaxel, AA and enzalutamide were evaluated in patients with mCRPC with disease progression during or after docetaxel treatment in separate randomized Phase III trials – TROPIC, COU-AA-301 and AFFIRM, respectively (Table 1).

Cabazitaxel (TROPIC)

Cabazitaxel was the first agent to demonstrate improved survival post-docetaxel in mCRPC patients. The approval of cabazitaxel was based on the TROPIC study, a randomized, open-label, Phase III trial in 755 patients with mCRPC whose disease had progressed during or after treatment with a docetaxel-containing regimen (TROPIC; Table 1) [18]. Patients were randomized (1:1) to cabazitaxel (25 mg/m^2 1-h intravenous [IV] infusion every 3 weeks) plus prednisone (10 mg daily) or mitoxantrone (12 mg/m^2 IV infusion every 3 weeks) plus prednisone (10 mg daily). Eligible patients had pathologically proven prostate cancer, previous and ongoing castration by orchiectomy or luteinizing hormone-releasing hormone agonists, or both, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Patients with measurable disease were required to have documented disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) with $\geqslant 1$ visceral or soft-tissue metastatic lesion. Patients with non-measurable disease were required to have rising serum PSA concentrations (at least two consecutive increases relative to a reference value measured at least a week apart) or the appearance of at least one new demonstrable radiographic lesion. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), tumor response rate, PSA response rate and time to tumor progression (Table 1). For PFS, progression was indicated by any of PSA progression, tumor progression (radiologic evidence by RECIST) or pain.

Abiraterone acetate (COU-AA-301)

AA was evaluated in COU-AA-301, a randomized, double-blind, Phase III trial in 1195 patients with mCRPC who had previously received docetaxel and had progressive disease (Table 1) [19]. In this trial, patients were randomized (2:1) to AA (1 g orally, once daily) plus prednisone (5 mg twice daily) or placebo plus prednisone (5 mg twice daily). Eligible patients had histologically or cytologically confirmed prostate cancer, ongoing androgen deprivation, with a serum testosterone level of 50 ng per deciliter or less ($\leqslant$2.0 nmol per liter), and an ECOG PS of 0–2. Disease progression was defined according to the criteria of the Prostate Cancer Clinical Trials Working Group (PCWG2) [20] (two consecutive increases in PSA concentration over a reference value) or radiographic evidence of disease progression in soft tissue or bone with or without disease progression on the basis of the PSA value. The primary endpoint was OS; secondary endpoints included PFS, PSA progression, PSA response rate and QoL measures (Table 1). Before completion, the study was unblinded at the request of the Independent Data Monitoring Committee (IDMC) and patients receiving placebo were crossed over to receive active treatment [19].

Enzalutamide (AFFIRM)

Most recently approved by both the FDA (August 2012) and EMA (June 2013), enzalutamide (160 mg orally, once daily) was evaluated in AFFIRM, a randomized, double-blind, placebo-controlled, Phase III trial, which included 1199 patients with mCRPC who had previously been treated with docetaxel and had progressive disease, and who were randomized (2:1) to enzalutamide or placebo (Table 1) [21]. Patients had a histologically or cytologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng per deciliter [1.7 nmol per liter]) and an ECOG PS of 0–2. Progressive disease was defined according to PCWG2 [20] criteria and included three increasing values for PSA or radiographically confirmed progression with or without a rise in the PSA level. The primary endpoint was OS; secondary endpoints included PFS, time to first skeletal-related event (SRE), tumor response, PSA response and QoL measures (Table 1). After initial positive results from this trial, the study was terminated early at the request of the IDMC in order to cross patients over from placebo to active treatment [21].

Evaluation of the TROPIC, COU-AA-301 and AFFIRM trials

Study designs

Both the COU-AA-301 [19] and AFFIRM [21] trials were placebo controlled, in contrast to the TROPIC study [18], which compared cabazitaxel with mitoxantrone (a palliative chemotherapy). This

Table 1
Trial designs of the pivotal randomized Phase III trials of recently approved agents in metastatic castration-resistant prostate cancer progressing on or after docetaxel therapy.

Trial	Agent(s)	Comparator	Treatment regimen	Design	Sites	N	Primary endpoint	Main secondary endpoints
TROPIC [18]	Cabazitaxel + prednisone(10 mg daily) Randomized 1:1	Mitoxantrone (12 mg/m^2 IV infusion every 3 weeks) + prednisone	25 mg/m^2 1-h IV infusion every 3 weeks	OL	146 sites in 26 countries	755	OS	• PFS[b] • Time to tumor progression. • Time to PSA progression. • Time to pain progression. • PSA response. • Objective response. • Pain response
COU-AA-301 [19]	Abiraterone + prednisone(5 mg BID) Randomized 2:1	Placebo + prednisone	1 g orally, OD	DB	147 sites in 13 countries	1195	OS	• PSA response rate. • Time to PSA progressionPFS[c]. • QoL
AFFIRM [21]	Enzalutamide[a] Randomized 2:1	Placebo	160 mg orally, OD	DB	156 sites in 15 countries	1199	OS	• PFS[c] • Time to first SRE. • PSA response. • Objective soft tissue response. • QoL

BID, twice daily; DB, double blind; IV, intravenous; OD, once daily; OL, open label; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; QoL, quality of life; SRE, skeletal-related event.
[a] Use of prednisone or other glucocorticoids was permitted but not required.
[b] Progression defined as either PSA progression, tumor progression or pain progression.
[c] Radiographic progression.

fundamental difference makes cross-trial comparisons challenging. In future, the use of placebo-controlled trials in the second-line setting is unlikely to be possible on ethical grounds because the standard of care has changed following the approval of the newer agents [22].

In the TROPIC and COU-AA-301 trials, patients in both arms received prednisone treatment. In contrast, in the AFFIRM trial, the use of prednisone or other glucocorticoids was permitted, but not required. This may result in a heterogeneous population in terms of additional treatment administered, which may have an effect on the observed adverse events (AEs) and comparative efficacy between groups.

OS was the primary endpoint in all three trials; however, the selection and definition of secondary endpoints varied across the trials (Table 1). For example, in evaluation of PFS in the TROPIC study, progression was defined as any of the following: PSA progression, tumor progression (radiologic evidence by RECIST) or pain progression [18]. In contrast, the COU-AA-301 trial and the AFFIRM trial defined progression only as radiologic evidence of tumor progression by RECIST. As a result, treatment may have been stopped at an earlier point in the TROPIC study compared with the other trials, resulting in a shorter duration of treatment. The median duration of treatment was 8.0 and 8.3 months in the groups that received AA and enzalutamide, respectively, compared with an average of six treatment cycles (18 weeks) in patients receiving cabazitaxel in the TROPIC study [18,19,21].

Other differences in secondary endpoints and exploratory analyses included QoL and time to first SRE, which were both recorded in the COU-AA-301 and AFFIRM trials, but not the TROPIC trial. However, the TROPIC trial evaluated relief of tumor-related symptoms, such as pain response and time to pain progression. In addition, pain-related assessments were extensively evaluated in the COU-AA-301 and AFFIRM trials.

Study population

Global representation. Compared with AFFIRM [21] and COU-AA-301 [19], patients were enrolled into TROPIC [18] from a wider variety of regions (26 countries for TROPIC vs. 15 for AFFIRM and 13 for COU-AA-301). Conversely, the COU-AA-301 [19] and AFFIRM studies had larger patient populations than TROPIC [18] (N = 1195, N = 1199 and N = 755, respectively).

Baseline characteristics. All three trials recruited patients with progressive disease (including both patients with measurable progressive disease by RECIST and patients with progressive disease based on PSA increase), an ECOG PS of 0–2, and prior treatment with docetaxel [18,19,21]. However, the percentage of patients discontinuing prior treatment with docetaxel because of progression was higher in the TROPIC trial than in the COU-AA-301 trial (63% and 45% of patients who received cabazitaxel or AA, respectively) [23,24], suggesting that the patient population in TROPIC potentially had a higher degree of resistance to docetaxel. In addition, the TROPIC and AFFIRM trials also included patients who were more heavily pre-treated, with a subset having received >2 lines of prior chemotherapy (6.0% in the cabazitaxel arm of TROPIC and 3.1% in the enzalutamide arm of AFFIRM) [18,21], whereas the COU-AA-301 trial included only patients who had received either one or two previous regimens [19]. The TROPIC study also documented the time from last prior therapy to progression and from last prior therapy to randomization, providing a clearer description of the extent of disease burden for the study population [18,23]. The median time from last docetaxel dose to progression was 0.8 months and the majority (62%) of patients were randomized to cabazitaxel within 6 months of their last docetaxel treatment in the TROPIC trial [18,23]. Details of time from last prior therapy to progression or randomization in the COU-AA-301 and AFFIRM trial have not been published; therefore, less is known about the population and the extent of their disease burden. More detailed information on patient baseline characteristics may help clinicians when selecting the most appropriate agent to use in specific patient populations.

Efficacy

In all three trials, an OS benefit was seen in the experimental arm compared with the control arm (Table 2). However, the improved OS for cabazitaxel plus prednisone in TROPIC was compared with mitoxantrone plus prednisone (15.1 vs. 12.7 months; HR 0.70; 95% confidence interval [CI] 0.59–0.83; $P < 0.0001$) [18], whereas the improved OS for AA plus prednisone in COU-AA-301 was compared with placebo plus prednisone (14.8 vs. 10.9 months [HR 0.65; 95% CI 0.54–0.77; $P < 0.001$]) [19], and for enzalutamide in AFFIRM was compared with placebo alone (18.4 vs. 13.6 months [HR 0.63; 95% CI 0.53–0.75; $P < 0.001$]) [21] (Table 2). It is important to note that survival durations cannot be directly compared

between trials due to differences in the trial populations. The median duration of follow-up was 12.8 months in TROPIC and COU-AA-301, and 14.4 months in AFFIRM.

An updated analysis of OS in the COU-AA-301 trial has also been published, in which the difference in median OS between the two groups improved from 3.9 months [19] to 4.6 months (15.8 months for AA plus prednisone vs. 11.2 months for placebo plus prednisone; HR 0.74; $P < 0.0001$; median follow-up 20.2 months) [25].

Subgroup analyses reveal potential differences in OS outcomes depending on patient characteristics, although significance is difficult to measure due to small patient numbers in some subgroups. In particular, stratified analysis of the AFFIRM data found that enzalutamide did not significantly increase OS in patients with visceral metastases (poor prognosis) at baseline (HR 0.78; 95% CI 0.56–1.09) or in patients who had received two or more prior chemotherapy regimens (HR 0.74; 95% CI 0.54–1.03) [21]. Cabazitaxel also did not significantly increase OS in patients with visceral disease (HR 0.88; 95% CI 0.64–1.22) [26]. However, patients with visceral metastases derived a significant OS benefit from AA (HR 0.70; 95% CI 0.52–0.94) in the COU-AA-301 trial [19]. In both the TROPIC and COU-AA-301 trials, HRs in patients receiving more than one prior therapy (HR 0.75; 95% CI 0.55–1.02 for TROPIC [18], HR 0.74; 95% CI 0.55–0.99 for COU-AA-301) [19] were similar to the AFFIRM trial [21].

All three trials showed a significant median OS improvement in patients with ECOG PS 0–1 (HR 0.68; 95% CI 0.57–0.82 for TROPIC [18], HR 0.64; 95% CI 0.53–0.78 for COU-AA-301 [19], HR 0.62; 95% CI 0.52–0.75 for AFFFIRM) [21]. Conversely, the difference in median OS between treatment arms in patients with ECOG PS 2 did not reach significance in any of the trials (HR 0.81; 95% CI 0.48–1.38 for TROPIC [18], HR 0.81; 95% CI 0.53–1.24 for COU-AA-301 [19], HR 0.65; 95% CI 0.39–1.07 for AFFIRM) [21]; however, sample sizes for this subgroup were relatively small ($n = 61$, $n = 127$ and $n = 102$ in TROPIC, COU-AA-301 and AFFIRM, respectively).

In all trials, a significant OS benefit versus comparator was noted in patients ⩾65 years [18,19,21]. In COU-AA-301 and AFFIRM, a significant OS benefit was also noted in patients <65 years [19,21], whereas in TROPIC, although an OS benefit for cabazitaxel was indicated in patients aged <65 years, the difference between treatment arms was not statistically significant [18].

The TROPIC trial also analyzed OS benefit by total prior docetaxel dose, with significant benefit versus mitoxantrone noted in patients with total prior docetaxel doses of ⩾225–450 mg/m^2 (HR 0. 60; 95% CI 0.43–0.84) and ⩾900 mg/m^2 (HR 0.51; 95% CI 0.33–0.79).

All major secondary efficacy endpoints were met in all three trials (Table 2), although because of differences in trial design and definition of endpoints, data cannot be directly compared. Of note, unlike the COU-AA-301 and AFFIRM trials, in which progression was defined as radiographic progression (by RECIST) only, progression in TROPIC was defined as any of several criteria, resulting in a relatively short duration of PFS (2.8 months for cabazitaxel plus prednisone vs. 1.4 months for mitoxantrone plus prednisone; $P < 0.0001$) [18] (Table 2). In routine clinical practice, the definition of progression is likely to be somewhere between these two definitions, probably based on two of the three factors (PSA progression, tumor progression and pain progression). Time to tumor progression in TROPIC (by RECIST only) in patients with measurable disease (8.8 months for cabazitaxel plus prednisone [$n = 201$] vs. 5.4 months for mitoxantrone plus prednisone [$n = 204$]; $P < 0.0001$) was longer than PFS in the overall patient population, [18] and was similar to the PFS durations seen in the other trials (COU-AA-301: 5.6 months for AA plus prednisone vs. 3.6 months for placebo plus prednisone, $P < 0.001$ [19]; AFFIRM: 8.3 months for enzalutamide vs. 2.9 months for placebo, $P < 0.001$) (Table 2).

In AFFIRM, the time to first SRE was significantly prolonged in the enzalutamide group compared with placebo (16.7 months vs. 13.3 months, $P < 0.001$) [21]. In COU-AA-301, the proportion of patients with SRE was similar across the two treatment groups. However, the median time to first SRE was significantly longer in the AA arm than in the placebo arm (25.0 months vs. 20.3 months; $P = 0.0001$) [27]. Time to first SRE was not evaluated in the TROPIC trial [18].

Interestingly, pain response rate and time to pain progression were similar in the cabazitaxel and mitoxantrone groups in the TROPIC trial [18]. As mitoxantrone is an established palliative care option in this treatment setting, this suggests that cabazitaxel may have important palliative effects in addition to the OS benefit provided. In COU-AA-301, AA plus prednisone was associated with a higher rate of palliation of both pain intensity (45.0% vs. 28.8%, respectively; $P = 0.0005$) and pain interference with daily activities (60.1% vs. 38.0%, respectively; $P = 0.0002$) than placebo plus prednisone [27]. The AA arm was also superior to the placebo arm on several other measures of pain response. These included median time to palliation of pain intensity and pain interference, median time to progression of pain intensity and pain interference, and median duration of pain palliation [27]. Pain response/progression were not included as secondary endpoints in the AFFIRM trial [21].

Fatigue is commonly observed in patients with advanced prostate cancer [28]. The COU-AA-301 trial was the first Phase III trial in advanced prostate cancer to include an assessment of the effect of administered treatments on patient-reported fatigue intensity and fatigue interference with daily activities [29]. AA plus prednisone was shown to significantly increase the proportion of patients

Table 2
Comparison of the main efficacy results in the TROPIC [18], COU-AA-301 [19] and AFFIRM [21] trials.

Trial	Treatment arms	Primary endpoint: median OS, months	Main secondary efficacy endpoints			
			Tumor response rate, %[b]	PSA response rate, %[c]	Median PFS, months	Median time to PSA progression, months
TROPIC [18]	Cabazitaxel + prednisone vs. mitoxantrone + prednisone	15.1 vs. 12.7; HR 0.70 (0.59–0.83); $P < 0.0001$	14.4 vs. 4.4; $P = 0.0005$	39.2 vs. 17.8; $P = 0.0002$	2.8 vs. 1.4;[d] HR 0.74 (0.64–0.86) $P < 0.0001$	6.4 vs. 3.1; HR 0.75 (0.63–0.90) $P = 0.001$
COU-AA-301 [19]	Abiraterone + prednisone vs. placebo + prednisone	14.8 vs. 10.9; HR 0.65 (0.54–0.77); $P < 0.001$[a]	14.0 vs. 2.8; $P < 0.0001$	29.1 vs. 5.5; $P < 0.001$	5.6 vs. 3.6;[e] HR 0.67 (0.59–0.78) $P < 0.001$	10.2 vs. 6.6; HR 0.58 (0.46–0.73) $P < 0.001$
AFFIRM [21]	Enzalutamide vs. placebo	18.4 vs. 13.6; HR 0.63 (0.53–0.75); $P < 0.001$	29 vs. 4; $P < 0.001$	54 vs. 2; $P < 0.001$	8.3 vs. 2.9;[e] HR 0.40 (0.35–0.47) $P < 0.001$	8.3 vs. 3.0; HR 0.25 (0.20–0.30) $P < 0.001$

95% confidence intervals reported for hazard ratios.
HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
[a] Updated OS analysis:15.8 months for abiraterone vs. 11.2 months for placebo; HR 0.74; $P < 0.0001$ [25].
[b] In patients with measurable disease.
[c] Reduction in serum PSA by ⩾50%.
[d] Progression defined as either PSA progression, tumor progression or pain progression. Time to tumor progression was 8.8 vs 5.4 months; HR 0.61 (0.49–0.76); $P < 0.0001$.
[e] Radiographic progression.

reporting improvement in fatigue intensity (58.1% vs. 40.3%, respectively; $P = 0.0001$) and improved fatigue interference (55.0% vs. 38.0%, respectively; $P = 0.0075$) compared with placebo plus prednisone [29]. Time to progression of fatigue was also significantly prolonged in the AA arm compared with the placebo arm. Measures of fatigue were not included in the AFFIRM or TROPIC trials [18,21].

The QoL response rate, assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire [30], was increased vs. placebo in the AFFIRM trial (43% for enzalutamide vs. 18% for placebo; $P < 0.001$). Although QoL data were collected in the COU-AA-301 trial, these have not yet been reported. QoL data were not collected in the TROPIC study.

Safety

A comparison of the main safety results of the TROPIC, COU-AA-301 and AFFIRM trials is shown in Table 3. The TROPIC trial demonstrated that cabazitaxel treatment was associated with hematologic and gastrointestinal AEs, manageable with prophylactic granulocyte-colony stimulating factor (G-CSF) use and proactive patient monitoring [18]. G-CSF and loperamide support for patients with neutropenia or diarrhea, respectively, was specified in the study protocol, with the exception of use during Cycle 1. Other AEs reported in the TROPIC trial were consistent with those expected for taxane-based therapies such as docetaxel and paclitaxel. Anemia was the most common AE in the cabazitaxel group (all grades, 97% in the cabazitaxel group vs. 81% in the mitoxantrone-group; Grade $\geqslant 3$, 11% vs. 5%), followed by leukopenia (all grades, 96% vs. 92%; Grade $\geqslant 3$, 68% vs. 42%) and neutropenia (all grades, 94% vs. 88%; Grade $\geqslant 3$, 82% vs. 58%) [18]. Grade $\geqslant 3$ febrile neutropenia occurred in 8% of patients receiving cabazitaxel and 1% of patients receiving mitoxantrone. The most common non-hematologic AEs were diarrhea (all grades, 47% in the cabazitaxel group vs. 11% in the mitoxantrone group; Grade $\geqslant 3$, 6% vs. <1%) and fatigue (all grades, 37% vs. 27%; Grade $\geqslant 3$, 5% vs. 3%). Grade 3 peripheral neuropathy was uncommon (1% in both treatment groups). Eighteen percent of patients discontinued treatment due to AEs in the cabazitaxel group compared with 8% in the mitoxantrone group. Dosereductions occurred in 10% of patients receiving cabazitaxel compared with 5% of patients receiving mitoxantrone. Total deaths during the study were 227 (61%) in the cabazitaxel group compared with 275 (74%) in the mitoxantrone arm. The most frequent cause of death due to AEs in the cabazitaxel group was neutropenia and its clinical consequences/sepsis (7 patients [2%] compared with 1 patient [<1%] in the placebo group).

Interim results ($n = 919$) from a compassionate-use program and expanded-access program of cabazitaxel plus prednisone in patients with mCRPC previously treated with docetaxel reported lower rates of AEs (including febrile neutropenia) compared with TROPIC [31]. The most common relevant Grade 3/4 AEs possibly related to cabazitaxel were febrile neutropenia (6.1%), fatigue (3.6%), diarrhea (3.0%) and nausea (1.0%) ($n = 919$).

The COU-AA-301 study demonstrated that urinary tract infections were more common in patients who received AA compared with patients who received placebo (all grades, 12% vs. 7%; Grade 3, 2% vs. <1%) [19]. Furthermore, treatment with AA was associated with elevated mineralocorticoid levels; fluid retention and edema were increased in the AA group compared with placebo (all grades,

Table 3
Comparison of the main safety results in the TROPIC [18], COU-AA-301 [19] and AFFIRM [21] trials.

Adverse event	TROPIC (cabazitaxel + prednisone arm; $n = 371$)		COU-AA-301 (abiraterone + prednisone arm; $n = 791$)		AFFIRM (enzalutamide arm; $n = 800$)	
Hematologic	All grades	Grades $\geqslant 3$	All grades	Grades 3/4	All grades	Grades $\geqslant 3$
Anemia	361 (97)	39 (11)	178 (23)	59 (7)	N/A	N/A
Thrombocytopenia	176 (47)	15 (4)	28 (4)	11 (1)	N/A	N/A
Leukopenia	355 (96)	253 (68)	N/A	N/A	N/A	N/A
Neutropenia	347 (94)	303 (82)	7 (1)	1 (<1)	N/A	N/A
Febrile neutropenia	0	28 (8)	0	0	N/A	N/A
Non-hematologic						
Abdominal pain	43 (12)	7 (2)	95 (12)	16 (2)	N/A	N/A
Arthralgia	39 (11)	4 (1)	215 (27)	33 (4)	N/A	N/A
Asthenia	76 (20)	17 (5)	104 (13)	18 (2)	N/A	N/A
Back pain	60 (16)	14 (4)	233 (30)	47 (6)	N/A	N/A
Bone pain	19 (5)	3 (1)	194 (25)	44 (6)	N/A	N/A
Cardiac disorder	N/A		106 (13)	33 (4)	49 (6)	7 (1)
Constipation	76 (20)	4 (1)	206 (26)	8 (1)	N/A	N/A
Diarrhea	173 (47)	23 (6)	139 (18)	5 (<1)	171 (21)[a]	9 (1)[a]
Dyspnea	44 (12)	5 (1)	102 (13)	10 (1)	N/A	N/A
Fatigue	136 (37)	18 (5)	346 (44)	66 (8)	269 (34)[a]	50 (6)[a]
Fluid retention and edema	N/A	N/A	241 (31)	18 (2)	N/A	N/A
Headache	N/A	N/A	N/A		93 (12)[a]	6 (<1)[a]
Hematuria	62 (17)	7 (2)	65 (8)	11 (1)	N/A	N/A
Hypertension	N/A	N/A	77 (10)	10 (1)	N/A	N/A
Hypokalemia	N/A	N/A	135 (17)	30 (4)	N/A	N/A
Hot flash	N/A	N/A	N/A		162 (20)[a]	0[a]
Liver function abnormality[b]	N/A	N/A	81 (10)	27 (3)	8 (1)	3 (<1)
Musculoskeletal pain	N/A	N/A	N/A		109 (14)[a]	8 (1)[a]
Nausea	127 (34)	7 (2)	233 (30)	13 (2)	N/A	N/A
Pain	20 (5)	4 (1)	13 (2)	5 (1)	N/A	N/A
Pain in arm or leg	N/A	N/A	134 (17)	19 (2)	N/A	N/A
Pain in extremity	30 (8)	6 (2)	N/A	N/A	N/A	N/A
Pyrexia	45 (12)	4 (1)	71 (9)	3 (<1)	N/A	N/A
Seizure	N/A	N/A	N/A	N/A	5 (<1)	5 (<1)
Urinary tract infection	27 (7)	4 (1)	91 (12)	17 (2)	N/A	N/A
Vomiting	84 (23)	7 (2)	168 (21)	14 (2)	N/A	N/A

N/A = not available.
[a] These data are adverse events that occurred in more than 10% of patients in the enzalutamide group, and at a rate of at least 2% higher than in the placebo group.
[b] Included hyperbilirubunemia and increased levels of aspartate amino transferase.

31% vs. 22%; Grade 3, 2% vs. 1%; Grade 4, <1% vs. 0%) [19]. In patients who develop this AE, use of prednisone may not be advisable because of its intrinsic mineralocorticoid activity. AA treatment was also associated with elevated aminotransferase levels, resulting in a protocol amendment that specified more frequent liver function monitoring during the trial [19]. The most common AEs reported in the COU-AA-301 trial were fatigue (all grades, 44% in the AA group vs. 43% in the placebo group; Grade 3, 8% vs. 9%; Grade 4, <1% vs. 1%), back pain (all grades, 30% vs. 33%; Grade 3, 6% vs. 9%; Grade 4, <1% vs <1%) and nausea (all grades, 30% vs. 32%; Grade 3, 2% vs. 3%; Grade 4, <1% vs. 0%). AEs leading to treatment discontinuation occurred with similar frequency in both groups (19% in the AA group vs. 23% in the placebo group). The incidence of dose modifications due to AEs was also similar in both groups. In total, there were 333 deaths (42%) in the AA group and 219 deaths (55%) in the placebo group. Fewer AE-related deaths were reported in the AA group than in the placebo group (12% vs. 15%). Eleven percent of patients (actual numbers not reported) in the AA group and 13% of patients (actual numbers not reported) in the placebo group died within 30 days of last dose of study medication, themajority of whom died due to disease progression, indicating that time available to administer another treatment is limited.

In the AFFIRM trial, overall rates of AEs were similar in the enzalutamide and placebo groups, although rates of fatigue (all grades, 34% vs. 29%; Grade $\geqslant$ 3, 6% vs. 7%), diarrhea (all grades, 21% vs. 18%; Grade $\geq$3, 1% vs. <1%), hot flashes (all grades, 20% vs. 10%), musculoskeletal pain (all grades, 14% vs. 10%; Grade $\geq$3, 1% vs. <1%) and headache (all grades, 12% vs. 6%; Grade $\geq$3, <1% vs. 0%) were higher in the enzalutamide group compared with the placebo group [21]. Seizure was reported in 0.6% of patients in the enzalutamide group, whereas it was not reported in the placebo group [21]. Of the patients who experienced seizures in the enzalutamide group, several had factors potentiallypredisposing to seizure [21]. These results suggest that enzalutamide may not be the most appropriate agent for use in patients at risk of seizure. Eight percent of patients discontinued due to an AE in the enzalutamide group compared with 10% in the placebo group. The median time to the first Grade $\geq$3 AE was 12.6 months in the enzalutamide group compared with 4.2 months in the placebo group. There were 308 deaths (39%) in the enzalutamide group and 212 deaths (53%) in the placebo group. AEs leading to death occurred in 23 patients (3%) in the enzalutamide group and 14 patients (4%) in the placebo group.

Ongoing and recently completed studies of approved second-line agents in mCRPC

A trial of AA as a first-line treatment for mCRPC (COU-AA-302) has recently been published [32]. In the trial, 1088 chemotherapy-naïve, asymptomatic or mildly symptomatic patients were randomized to receive AA (1 g orally, once daily) plus prednisone (5 mg orally, twice daily) or placebo plus prednisone (5 mg orally, twice daily) [32]. The co-primary endpoints were radiographic PFS and OS. After favorable interim results, the study was unblinded and patients receiving placebo were crossed over to receive active treatment. At the time of interim analysis, the median radiographic PFS was 16.5 months in the AA group compared with 8.3 months in the placebo group (HR 0.53; 95% CI 0.45–0.62; $P < 0.001$). Median OS had not been reached in the AA group, and was 27.2 months (HR 0.75; 95% CI 0.61–0.93; $P = 0.01$) in the placebo group [32]. Based on results from this trial, AA has been approved by the FDA in combination with prednisone in the treatment of late-stage, castration-resistant prostate cancer before chemotherapy.

First-line enzalutamide is also being evaluated in a large, placebo-controlled Phase III trial in ~1680 chemotherapy-naïve patients with progressive mCRPC (PREVAIL; NCT01212991). The primary endpoints are OS and PFS; secondary endpoints include time to first SRE and time to initiation of cytotoxic therapy. The trial is reported to complete in 2014.

A large, open-label, randomized, Phase III dose-optimization trial of cabazitaxel in the docetaxel-refractory mCRPC setting is ongoing (NCT01308580). The PROSELICA study will randomize ~1200 patients to receive cabazitaxel 20 or 25 mg/m^2 IV every 3 weeks plus prednisone (10 mg orally, once daily) [33]. The primary endpoint is OS, and secondary endpoints include PFS, PSA progression and response, pain progression and response, tumor response, health-related QoL, safety, pharmacokinetics and pharmacogenomics. The trial is estimated to complete in 2017.

Cabazitaxel is also being evaluated in a first-line Phase III trial (FIRSTANA; NCT01308567). In this open-label trial, ~1170 patients with chemotherapy-naïve mCRPC will be randomized to docetaxel (75 mg/m^2 every 3 weeks) or cabazitaxel (20 or 25 mg/m^2 every 3 weeks) plus prednisone (10 mg orally, daily). The primary endpoint is OS and secondary endpoints include PFS, PSA progression-free survival, pain progression-free survival, tumor response, PSA response, pain response, time to first SRE, health-related QoL, pharmacokinetics and pharmacogenomics. The trial is estimated to complete in 2017.

A Phase I/II dose-escalation study of cabazitaxel (every 3 weeks) plus AA (1 g orally, daily) and prednisone (10 mg orally, daily) is also ongoing in ~38 patients with mCRPC whose disease has progressed after treatment with docetaxel (NCT01511536). The primary endpoints are the maximum tolerated dose and PSA response rate. Secondary endpoints include safety, objective PFS, PSA progression-free survival, objective response rate, OS and pharmacokinetics. This study, estimated to be completed in 2014, will potentially provide important information on the use of these agents in combination in this setting.

Overview of additional agents approved or in development for patients with mCRPC

Several Phase III trials of investigational agents in the second-line mCRPC setting are ongoing (Table 4). Initial results of a double-blind, randomized, Phase III trial of radium-223 (ALSYMPCA; ALpharadin in SYMptomatic Prostate CAncer patients) have been reported [16,17]. In the trial, 921 patients with mCRPC and $\geqslant$2 bone metastases, who were either previously treated with docetaxel or were unsuitable for, or declined, docetaxel, were randomized 2:1 to receive radium-223 treatment (50 kBq/kg; six IV administrations separated by 4-week intervals) plus best supportive care, or placebo plus best supportive care [16,17]. Radium-223 was found to improve OS compared with placebo and the study was terminated early at the request of the IDMC [34]. An analysis performed before patients in the placebo arm were crossed over to active treatment found a median OS of 14.9 months in the radium-223 group vs. 11.3 months in the placebo group (HR 0.70; 95% CI 0.58–0.83; $P = 0.00007$) [17]. Several secondary efficacy endpoints were also met, including a significant increase in time to first SRE compared with placebo (median 13.6 months vs. 8.4 months; HR 0.61; 95% CI 0.461–0.807; $P = 0.00046$) [35]. Because the ALSYMPCA trial included only patients with $\geqslant$2 bone metastases and excluded patients with visceral metastases, the patient population differed to those of the TROPIC, COU-AA-301 and AFFIRM trials [17]. Safety and tolerability of radium-233 were favorable; however, hematologic AEs, although rare, were increased in patients who received radium-223 [17]. Grade 3/4 neutropenia occurred in 2.2% and 0.7% of the radium-223 and placebo groups,

Table 4
Agents in Phase III randomized trials for metastatic castration-resistant prostate cancer progressing on or after docetaxel therapy.

Agent and trial	Class	Design	N	Treatment arms	Patient population	Primary endpoint	Main secondary endpoints
Radium-223 (50 kBq/kg IV every 4 weeks) ALSYMPCA (NCT00699751) [16,17]	Targeted alpha-emitter	DB	921	Radium-223 + BSC vs. placebo + BSC	Symptomatic CRPC with ⩾2 bone metastases, either post-docetaxel or unsuitable for/declined docetaxel	OS	• Time to first SRE. • Safety
Orteronel (400 mg BID) C21005 (NCT01193257) [36]	17,20-lyase inhibitor	DB	1083[a]	Orteronel + prednisone vs. placebo + prednisone	mCRPC that has progressed during or following docetaxel	OS	• Radiographic PFS. • PSA decrease of ⩾50% at 12 weeks. • Pain response at 12 weeks. • Safety. • Time to PSA progression. • Objective response. • Circulating tumor cells and endocrine marker changes. • PROs.
Ipilimumab (10 mg/kg IV every 3 weeks) CA184-043 (NCT00861614) [37]	Anti-CTLA-4 monoclonal antibody	DB	800[a]	RT + ipilimumab vs. RT + placebo	mCRPC with progression on or within 6 months of docetaxel; ⩾1 bone metastases appropriate for RT; ECOG PS 0–1	OS	• PFS. • Pain response. • Safety.

BID, twice daily; BSC, best standard of care; DB, double blind; ECOG, European Cooperative Oncology Group; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; PSA, prostate-specific antigen; RT, radiotherapy; SRE, skeletal-related event.
[a] Planned enrollment.

respectively, and Grade 3/4 thrombocytopenia occurred in 6.3% and 2% [17]. A full publication reporting the primary findings from the ALSYMPCA trial is awaited before the data can be evaluated further. However, the fact that the trial included patients unsuitable for, or who declined, docetaxel has important implications for the patient population who will likely derive benefit from this agent in clinical practice.

Summary and conclusions

The TROPIC, COU-AA-301 and AFFIRM trials have all reported significant improvements in OS in patients with mCRPC in the second-line setting. Patients now have several treatment options post-docetaxel, including the three agents evaluated in these trials (cabazitaxel, AA and enzalutamide). These developments represent major progress and have changed the standard of care. In the absence of sequencing data, clinicians need to decide which therapies to use based on existing evidence. Differences in study designs make it difficult to draw cross-trial comparisons.

However, more detailed information on patient baseline and disease characteristics, together with additional sequencing studies, may allow clinicians to identify specific populations that will benefit most from different drugs. For example, for patients who have not received prior docetaxel treatment, several agents have demonstrable activity, including abiraterone, enzalutamide and radium-223. These agents may be preferable to chemotherapy both in patients with asymptomatic disease and in patients with factors predisposing to poor tolerance of chemotherapy. On the other hand, for patients with rapidly progressing disease or visceral metastases, or patients with a poor response to initial androgen deprivation therapy, the use of chemotherapy may be preferred. A study investigating the use of cabazitaxel in the first-line setting is underway. For patients who have received prior docetaxel therapy, approved choices include abiraterone, cabazitaxel, enzalutamide and radium-223. In the absence of robust sequencing data and treatment guidelines, treatment choice may be guided by drug availability together with physician experience. In addition, patient characteristics such as performance status and response to and toxicities experiences with prior regimens should also be assessed. Across all treatment settings, it is reasonable that patients at risk of specific AEs should avoid certain agents; for example, patients at risk of seizure may be better suited to cabazitaxel or AA, rather than enzalutamide. As patients with mCRPC are a heterogeneous population, and the disease is highly dynamic, an adaptive approach may be required.

Systemic treatment for prostate cancer is changing rapidly and new treatments are already improving outcomes for men with mCRPC. Additional studies are needed to optimize the use of these agents by identifying those patients who most benefit and discovering the best way of giving them either in combination or as sequential single agents. Consideration of optimal sequencing strategies is important to maximize use of available therapies. In particular, switching to next treatment early upon disease progression is important to optimize patient benefit from all suitable therapeutic options.

Conflict of interest statement

Amit Bahl: Advisory boards and honoraria from Sanofi, Janssen, Astellas and Pfizer.

Susan Masson: Honoraria and travel grants from Sanofi.

Alison Birtle: Educational grant and advisory board honoraria from Sanofi. Advisory board honoraria from Janssen and Astellas.

Simon Chowdhury: Advisory boards for Sanofi and Janssen-Cilag.

Johann de Bono: Employed by the Institute of Cancer Research. Consultant/advisory role with Sanofi. Honoraria from Sanofi, Johnson & Johnson and Astellas. Research funding from Sanofi.

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References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer. 2010; Available from: <http://globocan.iarc.fr> [Accessed March 2013].

[2] National Comprehensive Cancer Network. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) Prostate Cancer (Version 3.2012). 2012; Available from: <http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf> [Accessed March 2013].

[3] Horwich A, Parker C, Bangma C, Kataja V. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(Suppl 5):v129–33.

[4] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, Mason MD, et al. Guidelines on Prostate Cancer. 2012; Available from: <http://www.uroweb.org/gls/pdf/08%20Prostate%20Cancer_LR%20March%2013th%20-2012.pdf> [Accessed March 2].

[5] Omlin A, Pezaro C, Mukherji D, et al. Improved Survival in a Cohort of Trial Participants with Metastatic Castration-resistant Prostate Cancer Demonstrates the Need for Updated Prognostic Nomograms. *Eur Urol* 64, 2013, 300–306.

[6] Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242–5.

[7] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.

[8] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513–20.

[9] Dumontet C, Sikic BI. Mechanisms of action of and resistance to antitubulin agents: microtubule dynamics, drug transport, and cell death. J Clin Oncol 1999;17:1061–70.

[10] O'Neill AJ, Prencipe M, Dowling C, et al. Characterisation and manipulation of docetaxel resistant prostate cancer cell lines. Mol Cancer 2011;10:126.

[11] JEVTANA® (cabazitaxel) Injection, Prescribing Information, FDA. Available from: http://products.sanofi.us/jevtana/jevtana.pdf [Accessed March 2013].

[12] JEVTANA® (cabazitaxel) Injection, Summary of Product Characteristics, EMA. <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002018/WC500104764.pdf> [Accessed March 2013].

[13] Janssen biotech. Zytiga (abiraterone acetate) tablets for oral administration, Prescribing Information, FDA. Available from: <http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf> [Accessed March 2013].

[14] Janssen biotech. Zytiga (abiraterone acetate) tablets for oral administration, Summary of Product Characteristics, EMA. Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002321/WC500112858.pdf> [Accessed March 2013].

[15] Astellas Pharma US I. Xtandi® (enzalutamide) capsules for oral use, Prescribing Information, FDA. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf [Accessed March 2013].

[16] Parker C, Heinrich D, O'Sullivan JM, et al. Overall survival benefit and safety profile of radium-223 chloride, a first-in-class alpha-pharmaceutical: results from a phase III randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) with bone metastases. J Clin Oncol 2012;30. Abstract 8.

[17] Parker C, Nilsson S, Heinrich D, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). J Clin Oncol 2012;30. Abstract LBA4512.

[18] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.

[19] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.

[20] Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.

[21] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.

[22] Antonarakis ES, Eisenberger MA. Expanding treatment options for metastatic prostate cancer. N Engl J Med 2011;364:2055–8.

[23] de Bono JS, Oudard S, Ozguroglu M, et al. A subgroup analysis of the TROPIC trial exploring reason for discontinuation of prior docetaxel and survival outcome of cabazitaxel in metastatic castration-resistant prostate cancer (MCRPC). J Clin Oncol 2011;29:2–18. Abstract 4526.

[24] Chi KN, Scher HI, Molina A, et al. Exploratory analysis of survival benefit and prior docetaxel (D) treatment in COU-AA-301 a phase III study of abiraterone acetate (AA) plus prednisone (P) in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2012;30. Abstract 15.

[25] Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.

[26] Oudard S, de Bono JS, Ozguroglu M, et al. Impact of cabazitaxel (CBZ) + prednisone (P; CBZP) on overall survival (OS) at 2 years and in patients (pts) with aggressive disease: post-hoc analyses of TROPIC trial. ESMO 2012. Abstract 933P.

[27] Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol 2012;13:1207–17.

[28] Carter N, Bryant-Lukosius D, DiCenso A, Blythe J, Neville AJ. The supportive care needs of men with advanced prostate cancer. Oncol Nurs Forum 2011;38:189–98.

[29] Sternberg CN, Molina A, North S, et al. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. Ann Oncol 2012;24:1017–25.

[30] Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997;50:920–8.

[31] Malik Z, Di Lorenzo G, Basaran M, et al. Cabazitaxel (Cbz) + prednisone (P; CbzP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D) interim results from compassionate-use programme (CUP) and early-access programme (EAP). Ann Oncol 2012;23. Abstract 931P.

[32] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.

[33] Eisenberger MA, Hardy-Bessard AC, Mourey L, et al. Comparison of two doses of cabazitaxel plus prednisone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel (D)-containing regimen. J Clin Oncol 2012;30. Abstract TPS4692.

[34] ALGETA press release – radium-223. 2011; Available from: <http://www.algeta.com/news/news-article/?articleId=1521246> [Accessed March 2013].

[35] Sartor AO, Heinrich D, O'Sullivan JM, et al. Radium-223 chloride [Ra-223] impact on skeletal-related events (SREs) and ECOG performance status (PS) in patients with castration-resistant prostate cancer (CRPC) with bone metastases: Interim results of a phase III trial (ALSYMPCA]. J Clin Oncol 2012;30. Abstract 4551.

[36] Dreicer R, Agus DB, Bellmunt J, et al. A phase III randomized, double-blind, multicenter trial comparing the investigational agent orteronel (TAK-700) plus prednisone (P) with placebo plus P in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or following docetaxel-based therapy. J Clin Oncol 2012;30. Abstract TPS4693.

[37] Drake CG, Scher HI, Bossi A, et al. CA184-043 A randomized double-blind phase III trial comparing ipilimumab versus placebo following a single dose of radiotherapy (RT) in patients (pts) with castration-resistant prostate cancer (CRPC) who have received prior treatment with docetaxel (D). J Clin Oncol 2012;30. Abstract TPS4689.

EXHIBIT W

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Researchers identify inhibitor that overcomes drug resistance in prostate cancer

Epigenetic modification of the androgen receptor gene contributes to the development of castration-resistant prostate cancer

Date: June 12, 2017

Source: H. Lee Moffitt Cancer Center & Research Institute

Summary: A newly discovered epigenetic mechanism can lead to the development of castration-resistant prostate cancer, new research demonstrates.

FULL STORY

Prostate cancer is the third most common cause of cancer-related death in men in the United States. It is estimated that 161,360 men will be diagnosed and more than 26,700 men will die from the disease in this year. The majority of these deaths are caused by prostate cancer that becomes resistant to initial therapy and spreads to other sites, called metastatic castration-resistant prostate cancer. In a study published in *Cancer Cell*, Moffitt Cancer Center researchers report that a newly discovered epigenetic mechanism can lead to the development of castration-resistant prostate cancer. They identified a novel drug that targets this epigenetic mechanism and may be able to combat the deadly form of the disease.

Uncontrolled activity of male hormones, called androgens, contributes to the development of prostate cancer. One of the primary ways doctors treat prostate cancer is by inhibiting the activity of androgens by either surgically removing the testicles or with drugs that decrease androgen levels or activity. Unfortunately, even though most patients have early success with anti-androgen treatments, many patients eventually develop metastatic castration-resistant prostate cancer within two to three years. Castration-resistant prostate cancer is more difficult to treat and cure because scientists are unsure how it develops resistance to anti-androgen therapies.

"Undoubtedly, the foremost reason for transient effectiveness of the androgen deprivation therapy is a poor understanding of the molecular mechanisms driving progression to castration-resistant prostate cancer, which in turn has hampered development of new therapeutics," explained Nupam P. Mahajan, PhD, associate member of the Chemical Biology and Molecular Medicine Program at Moffitt.

The Moffitt team performed an extensive set of experiments in prostate tumor cells and mice. They discovered a protein, called ACK1, also known as TNK2 that activates a pathway that causes the DNA-bound proteins called histones to undergo a type of modification called epigenetic modification. This modification was specifically accomplished by androgen receptor protein with the help of ACK1 around the region of the androgen receptor gene! This results in high levels and activity of the androgen receptor even when prostate cancer cells have been treated with anti-androgen therapy.

Following this discovery, the researchers developed a novel drug called (R)-9bMS that targets ACK1 and performed experiments to determine if it could block prostate cancer growth. They discovered that the ACK1 inhibitor blocked epigenetic modification of the androgen receptor gene and decreased its levels and activity. Importantly, the ACK1 inhibitor blocked the growth of prostate cancer cells that were resistant to the anti-androgen drug enzalutamide (also known as XTANDI) and decreased the growth of castration-resistant prostate tumors in mice.

"This discovery is highly relevant because almost two thirds of castration-resistant prostate cancer patients do not respond to enzalutamide. Overall, (R)-9bMS opens up as a new, and desperately needed, therapeutic option for those castration-resistant prostate cancer patients who either do not respond to enzalutamide or have acquired resistance, post-treatment," said Dr. Kiran Mahajan, the first author of this paper.

Story Source:

Materials provided by **H. Lee Moffitt Cancer Center & Research Institute**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Kiran Mahajan et al. **ACK1/TNK2 Regulates Histone H4 Tyr88-phosphorylation and AR Gene Expression in Castration-Resistant Prostate Cancer**. *Cancer Cell*, June 2017 DOI: 10.1016/j.ccell.2017.05.003

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Current Understanding of Resistance to Abiraterone and Enzalutamide in Advanced Prostate Cancer

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Associate Professor of Oncology and Urology
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H&O How common is resistance to abiraterone and enzalutamide in castration resistant prostate cancer (CRPC)?

ESA Approximately 15% to 25% of patients with CRPC do not respond to first-line treatment with either abiraterone (Zytiga, Janssen) or enzalutamide (Xtandi, Astellas/Medivation), meaning that their prostate-specific antigen (PSA) values do not decrease or their tumors do not regress. The other 75% to 85% of patients respond to abiraterone or enzalutamide initially, but a subsequent PSA increase or tumor progression occurs in nearly all of them with time. In the first-line CRPC setting, resistance typically develops after 9 to 15 months of treatment with either agent.

What is interesting is that patients who receive enzalutamide or abiraterone as first-line therapy and subsequently become resistant have only a 15% to 30% rate of response to the alternative agent as second-line CRPC treatment. That finding clearly shows that cross-resistance occurs between enzalutamide and abiraterone. Resistance to second-line therapy takes approximately 3 to 6 months to develop, so the duration of benefit of second-line CRPC therapy is decreased by at least 50% compared with that of first-line therapy.

H&O Do we understand what causes resistance?

ESA Resistance to enzalutamide and abiraterone is multifactorial, and we have only recently begun to understand the mechanisms behind it.

One way to consider abiraterone and enzalutamide resistance is to divide it into 3 biological categories (Figure). The first category is *reactivation or persistent activation of the androgen receptor (AR)*, which results in increased synthesis of androgen within the tumor and in the adrenal glands, the generation of *AR* mRNA splice variants, and the development of activating mutations of the *AR* gene.

AR bypass pathways, the second category, include glucocorticoid receptor activation and progesterone receptor activation. Both of these alternative steroid receptors may, in certain contexts, stimulate the transcription of androgen-responsive genes.

Androgen/AR-independent mechanisms, the third category, include multiple divergent mechanisms of resistance: mutation or inactivation of the tumor protein p53 gene *(TP53)* or retinoblastoma tumor suppressor gene *(RB)*; activation of the Wnt signaling pathway; loss of the phosphatase and tensin homolog tumor suppressor gene *(PTEN)*, which induces activation of the phosphoinositide 3-kinase (PI3K) and AKT pathway; and the transformation of classic prostate adenocarcinoma into a neuroendocrine or small-cell phenotype that is often associated with the amplification of N-Myc *(MYCN)* or Aurora kinase A *(AURKA)*. An additional mechanism that has been receiving a lot of attention recently is impairment of DNA damage repair pathways induced by mutations in the breast cancer type 2 susceptibility protein *(BRCA2)* and ataxia telangiectasia mutated *(ATM)* genes.

H&O How do the mechanisms of resistance to the 2 agents differ, and do some of them overlap?

ESA One mechanism of resistance that occurs with both drugs is upregulation of the cytochrome P-450 isoform 17 (CYP17) enzyme, which plays a key role in the synthesis of androgen by the adrenal glands and by the prostate cancer tumor cells themselves.

A second mechanism that is common to both agents is upregulation of the AR. This may occur because either the *AR* gene is amplified or the AR protein is overexpressed.

A third mechanism that is common to the 2 drugs is the emergence of *AR* splice variants, in which abnormal splicing of the *AR* messenger RNA (mRNA) leads to the formation of a prematurely truncated AR protein that is constitutively active in a ligand-independent fashion.

Regarding mechanisms of resistance that are unique to abiraterone, the first of these is the L702H mutation in the ligand-binding domain of *AR*, which results in activation of the AR by glucocorticoids such as prednisone. This activation causes resistance to abiraterone because abiraterone is usually prescribed in combination with prednisone.

The second of these is the T878A mutation in *AR*, which makes the AR responsive to progesterone. Abiraterone increases blood levels of progesterone, which can stimulate the AR if this mutation is present.

Regarding mechanisms of resistance that are unique to enzalutamide, the first of these is the F877L mutation, which is also in the ligand-binding domain of *AR*. This mutation converts enzalutamide from an antagonist into an agonist, so that enzalutamide stimulates rather than inhibits the AR in patients with this mutation.

The second mechanism of resistance to enzalutamide is induction of the glucocorticoid receptor. It has been shown that after enzalutamide inhibits the AR, the glucocorticoid receptor can sometimes take over its role —some people say that it "hijacks" the AR's androgen response elements in DNA. The result is that the glucocorticoid receptor activates the transcription of genes that allow the tumor to proliferate.

H&O What clinical studies have looked at these mechanisms of resistance?

ESA Most of the studies in patients with CRPC have focused primarily on *AR* mutations, *AR* amplification, *AR* splice variants, or the glucocorticoid receptor.

At least 2 prospective studies have looked at *AR* mutations, which occur in approximately 5% to 15% of patients receiving enzalutamide or abiraterone. The first study, which was published by Romanel and colleagues in *Science Translational Medicine* in 2015, looked at circulating tumor DNA in patients receiving abiraterone. The researchers found that outcomes with abiraterone were much better in patients who had the wild-type *AR* gene than in those who had either *AR*-activating mutations or *AR* amplification.

The second study, which was published by Azad and colleagues in *Clinical Cancer Research* in 2015, evaluated circulating tumor DNA in patients receiving enzalutamide or abiraterone. Much as in the previous study, the researchers found that patients with the wild-type *AR* gene had a better prognosis than did those who had either *AR*-activating mutations or *AR* amplification.

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Immunotherapy Combination Generates Responses Against Castration-Resistant Metastatic Prostate Cancer (https://www.mdanderson.org/newsroom/c resistant-prostate-cancer-responds-to-immunotherapy-combination.h00-159300678.html)

ASCO Weighs-In on Widespread Youth Tobacco Use; See the Latest National Youth Tobacco Survey Results (https://www.asco.org/advocacy-policy/asco-in-action/asco-weighs-widespread-youth-tobacco-use-see-latest-national-youth)

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Bio-Rad Releases First FDA-Cleared Digital PCR System and Test for Monitoring Chronic Myeloid Leukemia Treatment Response (https://www.marketwatch.com/press-release/bio-rad-releases-first-fda-cleared-digital-pcr-system-and-test-for-monitoring-chronic-myeloid-leukemia-treatment-response-2019-02-14)

Rainier Therapeutics Presents Data on Vofatamab in Patients with Advanced Urothelial Cell Carcinoma (Bladder Cancer) Previously Treated with Chemotherapy at ASCO GU 2019

Several prospective studies have looked at the importance of *AR* splice variants, which are abnormal splice isoforms of *AR* mRNA. The majority of these splice variants lead to a truncated AR protein that retains the transcriptionally active N-terminal domain but is missing the C-terminal domain, which contains the ligand-binding pocket to which all the androgens and anti-androgens bind. Despite absence of the ligand-binding domain, these splice variants function as ligand-independent transcription factors and can stimulate cancer growth. The most important of the splice variants in humans is AR-V7.

The first clinical study on *AR* splice variants in CRPC was conducted here at Johns Hopkins and was published in the *New England Journal of Medicine* in 2014. In that study, we prospectively evaluated 62 patients who were starting either enzalutamide or abiraterone for the first time and analyzed AR-V7 with a circulating tumor cell (CTC) assay that we had developed. We found that outcomes of treatment with enzalutamide and abiraterone were significantly worse in patients who harbored AR-V7 in their CTCs than in those who did not have detectable AR-V7 in their CTCs. The results of that study were supported by another trial, conducted in Germany. That study, which was performed by Steinestel and colleagues and published in *Oncotarget* in 2015, also found that the presence of AR-V7 in CTCs was a negative prognostic factor for response to enzalutamide and abiraterone.

Interestingly, the presence of AR-V7 does not appear to be associated with primary resistance to chemotherapeutic agents commonly used in prostate cancer, such as docetaxel and cabazitaxel (Jevtana, Sanofi-Aventis). In fact, emerging evidence suggests that patients with AR-V7 in their CTCs may be better served by treatment with a chemotherapeutic agent such as docetaxel or cabazitaxel than by treatment with enzalutamide or abiraterone. Therefore, AR-V7 may be one of the first markers for treatment selection that we have in CRPC, which is an exciting prospect. These data clearly require further prospective validation before AR-V7 can be used in routine clinical practice.

Regarding investigations of glucocorticoid receptor expression, an important study was published by Arora and colleagues in *Cell* in 2013. In that study, patients underwent a bone marrow biopsy immediately before and 8 weeks after starting treatment with enzalutamide. It was found that the glucocorticoid receptor protein was more likely to be detected in bone marrow by immunohistochemistry in the patients who had either primary or acquired resistance to enzalutamide, and higher levels of the protein were associated with worse outcomes. This was the first study in humans to suggest that glucocorticoid receptor expression may correlate with enzalutamide resistance in patients with CRPC.

H&O What strategies are used to overcome resistance?

ESA Primary resistance is difficult to prevent, but a number of different approaches attempting to delay acquired resistance are being studied. For example, a large phase 3 study being led by the Alliance for Clinical Trials in Oncology is comparing enzalutamide plus abiraterone vs enzalutamide alone as first-line treatment of CRPC, to see whether the combination of these 2 agents will be more effective at improving overall survival (NCT01949337). One of the rationales for this approach is that the combination of the 2 drugs might prevent or slow the emergence of acquired *AR* mutations and *AR* splice variants or induction of the glucocorticoid receptor.

Another potential strategy would be to use the 2 agents in the optimal sequence for reducing acquired resistance. In a large, randomized phase 2 trial that is being conducted by Dr Kim Chi and colleagues at the Vancouver Cancer Centre of the BC Cancer Agency in Canada, patients are randomly assigned to start with abiraterone or enzalutamide and then switch to the other agent after disease progression. This trial will inform us whether either sequence is superior to the other, and a number of biomarkers embedded in this study will help clarify resistance mechanisms (NCT02125357).

A third potential strategy would be to combine enzalutamide or abiraterone with a second agent to target one of the other resistance pathways. For example, several trials are now combining enzalutamide or abiraterone with a PI3K inhibitor or an AKT inhibitor to see whether this combination might delay the development of secondary resistance (NCT02215096, NCT02525068, and NCT01884285).

A fourth potential strategy, which may overcome resistance induced by the glucocorticoid receptor, would be to add the glucocorticoid receptor antagonist mifepristone to enzalutamide treatment. An ongoing phase 2 trial is randomly assigning patients to either enzalutamide alone or enzalutamide plus mifepristone to determine whether the combination will prolong responses and delay resistance (NCT02012296).

Another approach that we have begun to test here at Johns Hopkins is the use of high-dose testosterone in patients with CRPC that has become resistant to abiraterone or enzalutamide (NCT02090114). Preclinical work has supported the idea that exposing CRPC cells to very high doses of testosterone can induce cell death by causing double-strand breaks in DNA as well as by preventing DNA relicensing during the cell cycle. The first of these studies, which was published by Schweizer and colleagues in *Science Translational*

(https://www.rainierrx.com/wp-content/uploads/2019/02/Final-2.15.19-ASCO_GU-data-Release-Rainier.pdf)

U S Proposes Medicare Coverage For CAR T Cancer Therapies (https //www reuters com/article/us usa healthcare/u s proposes medicare coverage for car t cancer therapies idUSKCN1Q41QX? feedType RSS&feedName healthNews)

Tweets

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Medicine in 2015, found that monthly intramuscular injections of high-dose testosterone produced significant clinical responses in approximately half of patients with CRPC. One of our emerging hypotheses is that high-dose testosterone therapy may also work by eliminating *AR* splice variants.

H&O Can biomarkers be used to determine whether enzalutamide and abiraterone will work?

ESA This is an area of great interest right now. I would say that the 2 most promising clinical biomarkers are AR-V7 in circulating tumor cells and *AR* mutations in circulating tumor DNA. I predict that these will enter the clinic within the next 3 years, and it will be possible to use a simple blood test to determine whether a patient is a good candidate for enzalutamide or abiraterone treatment. For example, patients with normal (wild-type) *AR* would be very likely to benefit from either abiraterone or enzalutamide, those with an activating mutation in the *AR* gene might be resistant to one or the other agent, and those with AR-V7 splice variants might not respond to either agent. Of course, prospective studies will need to be carried out to validate the clinical utility of these biomarkers before they can be used to make clinical decisions. Such validation studies are ongoing (NCT02269982).

H&O What other studies are looking at ways to overcome resistance?

ESA Right now, a phase 3 trial is examining at whether enzalutamide or galeterone, an experimental AR antagonist, is more effective in patients with CRPC positive for AR-V7 (NCT02438007). Galeterone may be able to overcome resistance caused by *AR* splice variants by degrading the AR-V7 protein. In addition, a phase 1/2 trial is looking at the use of an experimental agent called EPI-506. EPI-506 is the first drug to target the N-terminal of the AR, which theoretically should inhibit both mutant *AR* and *AR* splice variants in patients with treatment-resistant CRPC (NCT02606123).

Ongoing trials are also investigating agents that might target activating mutations in the *AR* gene, such as the AR inhibitors ODM-201 (NCT02200614) and VT-464 (NCT02130700). These agents may have clinical activity in men with certain activating *AR* mutations. As we discussed earlier, researchers are also investigating whether mifepristone, a glucocorticoid receptor inhibitor, can improve results in patients receiving enzalutamide. Moreover, a trial that is being led by Dr Gerhardt Attard at the Royal Marsden Institute in London is studying the use of onapristone, an agent that blocks the activated progesterone receptor, in patients with metastatic CRPC (NCT02049190).

Finally, in terms of AR-independent mechanisms of escape from abiraterone and enzalutamide, the experimental AURKA inhibitor alisertib is being studied as a possible way to overcome resistance in patients with neuroendocrine prostate carcinoma (NCT01799278).

Disclosures

Emmanuel S. Antonarakis has served as a paid consultant/advisor for Janssen, Astellas, Sanofi, Dendreon, ESSA, and Medivation and has received research funding from Janssen, Johnson & Johnson, Sanofi, Dendreon, Exelixis, Genentech, Novartis, and Tokai. He is also the coinventor of a biomarker technology that has been licensed to Tokai.

Suggested Readings

Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*. 2014;371(11):1028-1038.

Antonarakis ES, Lu C, Luber B, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. *JAMA Oncol*. 2015;1(5):582-591.

Arora VK, Schenkein E, Murali R, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell*. 2013;155(6):1309-1322.

Azad AA, Volik SV, Wyatt AW, et al. Androgen receptor gene aberrations in circulating cell-free dna: biomarkers of therapeutic resistance in castration-resistant prostate cancer. *Clin Cancer Res*. 2015;21(10):2315-2324.

Romanel A, Gasi Tandefelt D, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. *Sci Transl Med*. 2015;7(312):312re10.

Schweizer MT, Antonarakis ES, Wang H, et al. Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: results from a pilot clinical study. *Sci Transl Med*. 2015;7(269):269ra2.

Silberstein JL, Taylor MN, Antonarakis ES. Novel insights into molecular indicators of response and resistance to modern androgen-axis therapies in prostate cancer. *Curr Urol Rep*. 2016;17(4):29.

Steinestel J, Luedeke M, Arndt A, et al. Detecting predictive androgen receptor modifications in circulating prostate cancer cells [published online April 23, 2015]. *Oncotarget*. http://dx.doi.org/10.18632/oncotarget.3925.

Category: Prostate Cancer (http://www hematologyandoncology.net/mmp_articletype/prostate-cancer/)
Tags: abiraterone (http://www hematologyandoncology.net/mmp_articlecategories/abiraterone/), **enzalutamide (http://www hematologyandoncology.net/mmp_articlecategories/enzalutamide/)**, **Prostate Cancer (http://www hematologyandoncology.net/mmp_articlecategories/prostate-cancer/)**

EXHIBIT Y

The New York Times | https://nyti.ms/QKbqoW

BUSINESS DAY

New Drug For Prostate Cancer Gets F.D.A. Nod

By ANDREW POLLACK AUG. 31, 2012

The Food and Drug Administration approved a new life-prolonging drug for men with late-stage prostate cancer on Friday, adding to an increasingly crowded field.

The new drug, which will be called Xtandi, was developed by Medivation, a small San Francisco pharmaceutical company, in partnership with the Japanese firm Astellas Pharma.

In clinical trials, men who received the drug, which was previously known as MDV3100, lived a median of 18.4 months, nearly five months longer than the median of 13.6 months for those who received a placebo.

While the approval was not a surprise, its timing was. The F.D.A. approved the drug after only a three-month review, three months ahead of the deadline in late November. This is fairly rare, although a number of other cancer drugs have been approved at least a month ahead of deadline in recent years.

"The need for additional treatment options for advanced prostate cancer continues to be important," Dr. Richard Pazdur, the director of the agency's cancer drug office, said in a statement.

Xtandi is one of several new prostate cancer drugs that have come to market in the last two years after a long fallow period. While the new drugs have been good for

Xtandi will cost $7,450 a month, Medivation said. That is higher than some analysts had expected.

Before 2004, the only drug shown to prolong the survival of men with advanced prostate cancer was the chemotherapy drug docetaxel. Now there are four others on the market — Jevtana from Sanofi, Provenge from Dendreon, Zytiga from Johnson & Johnson and Xtandi, which is known generically as enzalutamide.

Xtandi is expected to compete most directly with Zytiga. Both are pills, while the other drugs are given intravenously. And both are aimed at the same patient population — men whose cancer has spread elsewhere in the body or recurred despite treatment aimed at suppressing production of the hormone testosterone, which fuels prostate cancer growth.

Both drugs are approved for men who have already tried docetaxel, though both Medivation and Johnson & Johnson hope to eventually win approval for their drugs to be used before docetaxel, a potentially much larger market. Many patients would prefer to use the pills before having to try chemotherapy.

Zytiga prolonged median survival by 3.9 months, as initially reported, though Johnson & Johnson later updated that figure to 4.6 months. Zytiga, which was approved in April 2011, had worldwide sales of $432 million in the first six months of this year.

Xtandi and Zytiga have not been compared head-to-head in a clinical trial. But some analysts say Xtandi would have an edge because it does not have to be given with prednisone, a steroid, to minimize side effects, as Zytiga does.

Xtandi has its own side effects, however, the most worrisome being seizures, which were suffered by about 1 percent of men taking it in the clinical trial.

There are expected to be about 241,000 new cases of prostate cancer this year in the United States and about 28,000 deaths.

Many men are treated with drugs like Lupron that, in effect, induce a chemical

Xtandi works by blocking the downstream effects of the action of testosterone, rather than by turning off its production.

It is the first product to reach the market for Medivation. The company previously developed an old Russian antihistamine as a potential treatment for Alzheimer's disease, signing a big partnership with Pfizer. But that drug failed in late-stage clinical trials.

Shares of Medivation closed at $104.86 Friday, up nearly 8 percent. The share price is about six times as high as it was before Medivation announced the results of its clinical trial last November.

A version of this article appears in print on September 1, 2012, on Page B3 of the New York edition with the headline: New Drug For Prostate Cancer Gets F.D.A. Nod.

EXHIBIT Z

International Journal of Urology / Volume 24, Issue 6

Original Article: Clinical Investigation | Free Access

Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant prostate cancer: The Kyoto-Baltimore collaboration

Naoki Terada, Benjamin L Maughan, Shusuke Akamatsu, Takashi Kobayashi, Toshinari Yamasaki, Takahiro Inoue, Tomomi Kamba, Osamu Ogawa, Emmanuel S Antonarakis

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Cited by: 8

Abstract

Objectives

To evaluate and compare the efficacy of sequential treatment with abiraterone followed by enzalutamide or vice versa for castration-resistant prostate cancer.

Methods

We retrospectively evaluated data on 198 consecutive chemotherapy-naïve patients who had received both abiraterone and enzalutamide for castration-resistant prostate cancer at Kyoto University Hospital (including satellite hospitals) and at Johns Hopkins Cancer Center. Prostate-specific antigen progression-free survival and overall survival in patients treated with sequential abiraterone-to-enzalutamide versus enzalutamide-to-abiraterone without intervening therapies were compared.

Results

Overall, 113 patients were treated with the abiraterone-to-enzalutamide sequence and 85 with the enzalutamide-to-abiraterone sequence. Median prostate-specific antigen progression-free survival was not significantly different between abiraterone and enzalutamide in the first-line setting (hazard ratio 0.88, 95% confidence interval 0.66–1.19, $P = 0.412$), but there was an advantage favoring enzalutamide compared with abiraterone in the second-line setting (hazard ratio 0.67, 95% confidence interval 0.49–0.91, $P = 0.009$). Furthermore, the combined prostate-specific antigen progression-free survival was significantly longer in the abiraterone-to-enzalutamide sequence than in the enzalutamide-to-abiraterone sequence (hazard ratio 0.56, 95% confidence interval 0.41–0.76, $P < 0.001$). The difference was significant even in multivariate analyses (hazard ratio 0.65, 95%

confidence interval 0.42–0.99, $P = 0.044$). There was no statistical difference in overall survival between the two sequences in univariate (hazard ratio 0.88, 95% confidence interval 0.53–1.43, $P = 0.599$) and multivariate analyses (hazard ratio 0.81, 95% confidence interval 0.49–1.35, $P = 0.427$).

Conclusions

The abiraterone-to-enzalutamide sequence might have more favorable efficacy in terms of combined prostate-specific antigen progression-free survival than the enzalutamide-to-abiraterone sequence, although no differences in overall survival were observed. This could possibly be attributable to longer prostate-specific antigen progression-free survival with second-line enzalutamide compared with abiraterone.

Abbreviations & Acronyms

ABI
: abiraterone

AR
: androgen receptor

CRPC
: castration-resistant prostate cancer

DTX
: docetaxel

ECOG
: Eastern Cooperative Oncology Group

ECOG PS
: Eastern Cooperative Oncology Group performance status

ENZ
: Aenzalutamide

LN
: lymph nodes

OS
: overall survival

PSA
: prostate-specific antigen

PSA-PFS
: prostate-specific antigen progression-free survival

Introduction

Prostate cancer is the second leading cause of cancer death in the USA[1] and the number of cases are rapidly increasing in Japan as well.[2] Patients presenting with advanced disease typically receive hormonal therapy using medical or surgical castration (with or without anti-

androgens) as initial treatment. However, most prostate cancer acquires resistance to the initial hormonal therapy over approximately 2–3 years, thus progressing to CRPC.[3]

Since DTX was introduced in 2004 to prolong the survival of patients with CRPC, there has recently been a rapid increase in the number of effective systemic agents for CRPC, including novel hormonal therapies, immunotherapies, chemotherapies and radiopharmaceutical drugs.[4] ABI is a CYP17 inhibitor, and ENZA is an anti-androgen targeting multiple steps in the AR signaling pathway. Recently, the metabolites of ABI have been shown to have an antagonistic effect on AR, and are considered to have further potential mechanisms of action.[5] In the USA, ABI was approved for CRPC in 2012, after showing improved OS in men with metastatic CRPC in the post-DTX and pre-DTX settings, respectively.[6, 7] This was followed quickly by the approval of ENZA, which also showed improved OS both before and after DTX.[8, 9] However, in Japan, ENZA was approved first for use in 2014, several months before ABI was approved. Although their mechanisms are different, the clinical efficacy of these drugs appears very similar. There are no reports yet that directly compare the efficacy of these two agents, although there are several retrospective studies showing the decreased efficacy of the second-line AR-targeting therapy after progression on the first-line therapy.[10, 11] This suggests that there are shared mechanisms of resistance between ABI and ENZA, such as AR-V7 splice variant expression and activating AR mutations[12, 13] as well as others.[12,13]

Currently, there is a trend to use these novel hormonal therapies before chemotherapy, because of better tolerability.[14] Elucidating an appropriate treatment sequence of these therapies is important for maximizing clinical benefit of CRPC patients. Therefore, we carried out a retrospective multi-institutional study in Japan (Kyoto) and the USA (Baltimore) to examine the potential differences in clinical outcomes between the treatment sequences of ABI-to-ENZA and ENZA-to-ABI.

Methods

The present study was an analysis of consecutive patients who received both ABI and ENZA for CRPC at Kyoto University Hospital including satellite hospitals (Kyoto, Japan) and the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD, USA). Only patients that received sequential therapy with ABI-to-ENZA or ENZA-to-ABI (without intervening treatments) were included in this analysis. All patients had pathologically proven adenocarcinoma of the prostate that was progressing according to serum PSA concentrations or radiographic criteria, despite androgen deprivation therapy. This study design was approved by the local institutional review boards of each center. Data were retrospectively obtained from paper and/or electronic medical records. For analysis of clinical outcomes, PSA progression was defined as an increase in PSA values by >25% relative to the baseline or nadir PSA value after ABI or ENZA treatment, as suggested by Prostate Cancer Working Group 2 criteria.[15] Combined PSA-PFS was measured from the start of the first novel hormonal therapy (ABI or ENZA) until

the time of PSA progression on the subsequent (second) AR-directed therapy. OS was defined as the time from initiation of ABI or ENZA treatment to death from any cause.

Descriptive data are presented as medians and ranges. PSA-PFS and OS (i.e. time-to-event outcomes) were estimated using the Kaplan–Meier method, and compared using univariate and multivariate Cox proportional hazard analyses, which were carried out to evaluate the optimal treatment sequence after adjusting for baseline clinical and demographic variables. In multivariate analyses, parameters significantly associated with survival in univariate analysis were included. Baseline characteristics were compared across groups using Fisher's exact tests and Mann–Whitney tests, as appropriate. All statistical analyses were carried out using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). *P*-values of <0.05 were considered statistically significant.

Results

Among 715 patients who had received both ABI and ENZA for CRPC (since 2011 at Johns Hopkins, and since 2014 at Kyoto University), 352 patients received sequential ABI and ENZA (or vice versa) without any intervening therapy: 163 patients received ABI-to-ENZA and 189 patients received ENZA-to-ABI. Baseline patient characteristics had some imbalances between the groups in terms of sequencing preferences (ABI-to-ENZA more common in USA, ENZA-to-ABI more common in Japan) and prior DTX treatment (29% in the ABI-to-ENZA group and 55% in the ENZA-to-ABI group). Therefore, we compared their treatment efficacy only in the DTX-naïve patients, 113 in ABI-to-ENZA group and 85 in ENZA-to-ABI group. Baseline patient characteristics are shown in Table 1, with some imbalances between the groups including number of prior anti-androgen treatment, such as bicalutamide, flutamide or estramustine (larger in ENZA-to-ABI group than in ABI-to-ENZA group). However, there was no difference in Gleason score, ECOG PS, rate of bone or visceral metastatic disease, or baseline PSA between groups.

Table 1. Patient baseline characteristics sequence in chemotherapy-naïve patients according to treatment

	ABI-to-ENZA sequence (*n* = 113)	ENZA-to-ABI sequence (*n* = 85)	*P*-value
Institution			
Kyoto University	29 (26%)	71 (84%)	<0.001
Johns Hopkins	84 (74%)	14 (16%)	
Gleason score			

	ABI-to-ENZA sequence (*n* = 113)	ENZA-to-ABI sequence (*n* = 85)	*P*-value
<8	32 (28%)	20 (24%)	0.518
8–10	70 (62%)	55 (65%)	
NA	11 (10%)	10 (11%)	
ECOG PS			
0–1	96 (85%)	73 (86%)	0.404
≥2	6 (5%)	8 (9%)	
NA	11 (10%)	4 (5%)	
Median, range PSA (ng/mL) at start of first agent	24.1 (0.79–2222)	17.0 (0.21–941)	0.175
Metastatic site			
No	21 (19%)	25 (29%)	0.575
LN	18 (16%)	11 (13%)	
Bone	66 (58%)	47 (55%)	
Visceral	8 (7%)	2 (2%)	
No. prior anti-androgen†			
0–1	68 (60%)	21 (25%)	<0.001
≥2	45 (40%)	64 (75%)	

†Includes estramustine. NA, not assessed.

PSA response rates were initially evaluated separately in first-line and second-line treatment settings in the ABI-to-ENZA and ENZA-to-ABI groups (Fig. 1). The >50% PSA response rates in the first-line setting were not significantly different in the ABI (48%) and ENZA (55%) groups (Fisher's exact test, $P = 0.353$). Conversely, the >50% PSA response rates in the second-line setting were significantly better in ENZA (29%) than the ABI (13%) group (Fisher's exact test, $P = 0.011$), suggesting that ENZA retains clinical activity after ABI, but that ABI is less effective after ENZA.

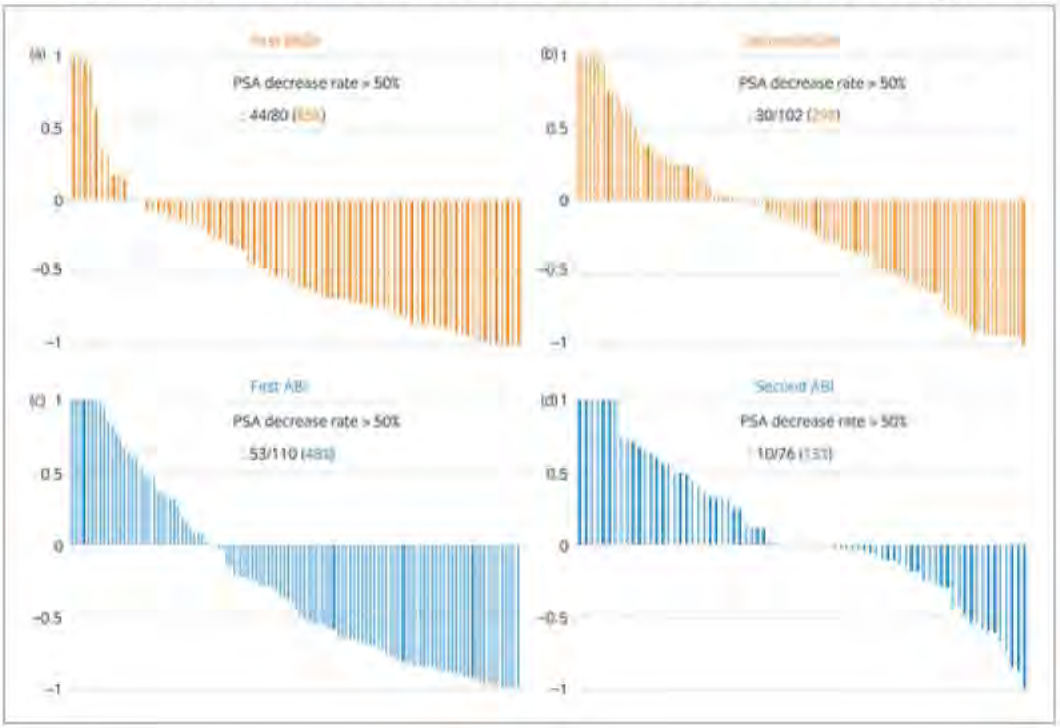

Figure 1

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Best PSA response rate in each sequence: (a) first-line ENZA, (b) second-line ENZA, (c) first-line ABI and (d) second-line ABI.

The PSA-PFS in the ABI-to-ENZA and ENZA-to-ABI groups was first analyzed in unadjusted Kaplan–Meier analysis. We assessed first-line and second-line therapy individually. In the first-line setting, there were no significant differences between ABI and ENZA with respect to PSA-PFS: 194 days (95% CI 137–250) versus 126 days (95% CI 105–165), respectively (HR 0.88, 95% CI 0.66–1.19, $P = 0.412$). In contrast, the median PSA-PFS for second-line ENZA was 91 days (95% CI 67–112), and was significantly longer than 55 days (95% CI 41–69) for second-line ABI (HR 0.67, 95% CI 0.49–0.91, $P = 0.009$; Fig. 2). Next, we compared the combined PSA-PFS in these two groups. The median combined PSA-PFS was 455 days (95% CI 385–495) in the ABI-to-ENZA sequence, and was significantly longer than 296 days (95% CI 235–358) in the ENZA-to-ABI sequence (HR 0.56, 95% CI 0.41–0.76, $P < 0.001$; Fig. 3a). These results suggest that the longer PSA-PFS durations with ABI-to-ENZA compared with ENZA-to-ABI might partially be explained by the efficacy (or lack thereof) of the second-line AR-directed agent, again implying that ENZA has more efficacy after ABI than vice versa.

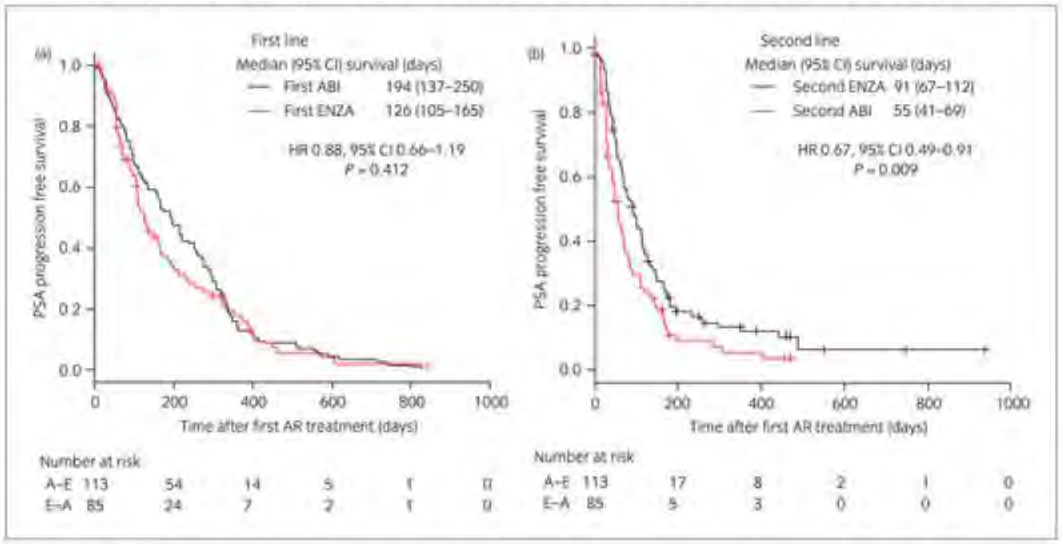

Figure 2

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PSA-PFS of ABI and ENZA as (a) first-line and (b) second-line treatments.

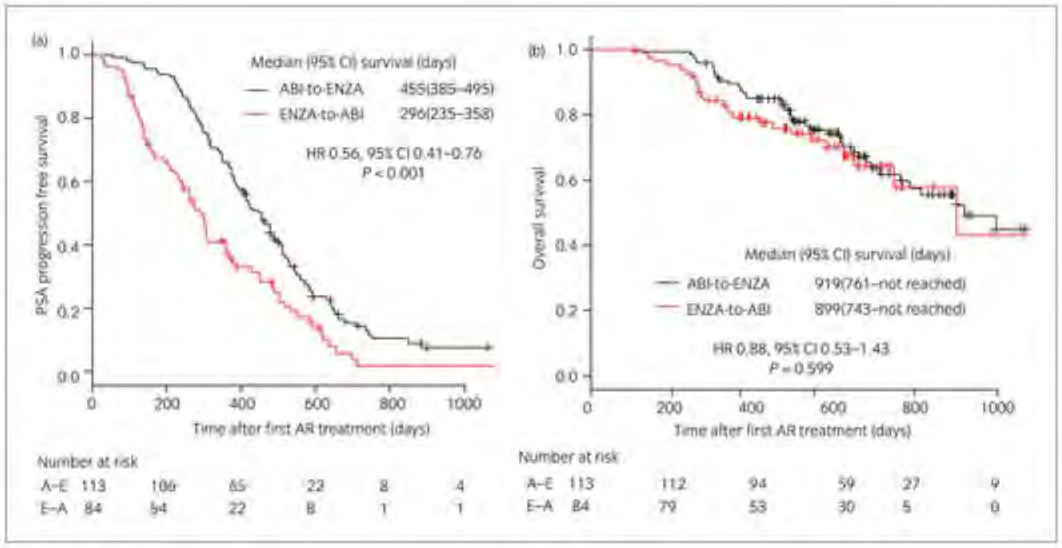

Figure 3

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(a) Combined PSA-PFS rate and (b) overall survival rate in the ABI-to-ENZA and ENZA-to-ABI sequences.

With respect to survival, the median OS was 919 days (95% CI 761–not reached) for the ABI-to-ENZA sequence, and 899 days (95% CI 743–not reached) for the ENZA-to-ABI sequence, a difference that was not statistically significant (HR 0.88, 95% CI 0.53–1.43, $P = 0.599$; Fig. 3b).

In order to adjust for baseline clinical and demographic factors, variables correlating with PSA-PFS and OS were evaluated by Cox proportional hazards analyses after including treatment

sequence (ENZA-to-ABI or ABI-to-ENZA), institution (Kyoto University or Johns Hopkins), Gleason score (<8 or 8–10), ECOG PS (0–1 or >1), baseline PSA (ng/mL), visceral disease (yes or no) and number of prior anti-androgen treatments (0–1 or ≥2). In univariate analysis, the treatment sequence of ABI-to-ENZA (HR 0.56, 95% CI 0.41–0.76, $P < 0.001$), the institution of Johns Hopkins (HR 0.54, 95% CI 0.40–0.74, $P < 0.001$) and higher Gleason score of 8–10 (HR 1.74, 95% CI 1.30–2.34, $P = 0.002$) were significantly correlated with PSA-PFS. In multivariate analysis including these parameters, the treatment sequence of ABI-to-ENZA (HR 0.65, 95% CI 0.42–0.99, $P = 0.044$) and higher Gleason score of 8–10 (HR 1.77, 95% CI 1.22–2.55, $P = 0.002$) were significant factors correlated with PSA-PFS (Table 2). Baseline PSA levels was significantly correlated with shorter OS in both univariate (HR 1.00, 95% CI 1.00–1.02, $P = <0.001$) and multivariate (HR 1.01, 95% CI 1.00–1.02, $P = 0.003$) analyses. The treatment sequence was not correlated with OS in univariate (HR 0.88, 95% CI 0.53–1.44, $P = 0.599$) and multivariable analysis (HR 0.81, 95% CI 0.49–1.35, $P = 0.427$; Table 3).

Table 2. Cox model for PSA progression-free survival

	Univariate			Multivariate		
	Hazard ratio	**95% CI**	***P*-value**	**Hazard ratio**	**95% CI**	***P*-value**
Treatment sequence						
ENZA-ABI	Ref [1.0]			Ref [1.0]		
ABI-ENZA	0.56	0.41–0.76	<0.001	0.65	0.42–0.99	0.044
Institution						
Kyoto University	Ref [1.0]			Ref [1.0]		
Johns Hopkins	0.54	0.40–0.74	<0.001	0.81	0.53–1.24	0.435
Gleason score						
<8	Ref [1.0]			Ref [1.0]		
8–10	1.74	1.30–2.34	0.002	1.77	1.22–2.55	0.002
ECOG PS						
0–1	Ref [1.0]					
>1	1.62	0.91–2.86	0.099			
Baseline PSA level						
Continuous variable	1.00	1.00–1.00	0.443			

	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Visceral disease						
No	Ref [1.0]					
Yes	1.07	0.52–2.18	0.859			
No. prior anti-androgens						
0–1	Ref [1.0]					
≥2	1.16	0.86–1.57	0.334			

Table 3. Cox model for OS

	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Treatment sequence						
ENZA-ABI	Ref [1.0]			Ref [1.0]		
ABI-ENZA	0.88	0.53–1.44	0.599	0.81	0.49–1.35	0.427
Institution						
Kyoto University	Ref [1.0]					
Johns Hopkins	1.07	0.64–1.78	0.796			
Gleason						
<8	Ref [1.0]					
8–10	1.34	0.77–2.31	0.301			
ECOG PS						
0–1	Ref [1.0]					
>1	1.73	0.74–4.02	0.207			
Baseline PSA Level						

	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Continuous variable	1.00	1.00–1.02	<0.001	1.00	1.00–1.01	<0.001
Visceral disease						
No	Ref [1.0]					
Yes	0.80	0.25–2.54	0.702			
No. prior anti-androgens						
0–1	Ref [1.0]					
≥2	0.65	0.40–1.06	0.084			

To elucidate the correlation of treatment efficacy between the sequence, PSA decrease rate and PSA-PFS time were compared between the first- and second-line therapy in each patient. PSA decrease rate and PSA-PFS time was not correlated between the first- and second-line sequence in both ABI-to-ENZA and ENZA-to-ABI groups (Fig. 4). These results showed that the second-line AR-targeting therapy might be effective even for the patients for whom first-line therapy was not effective.

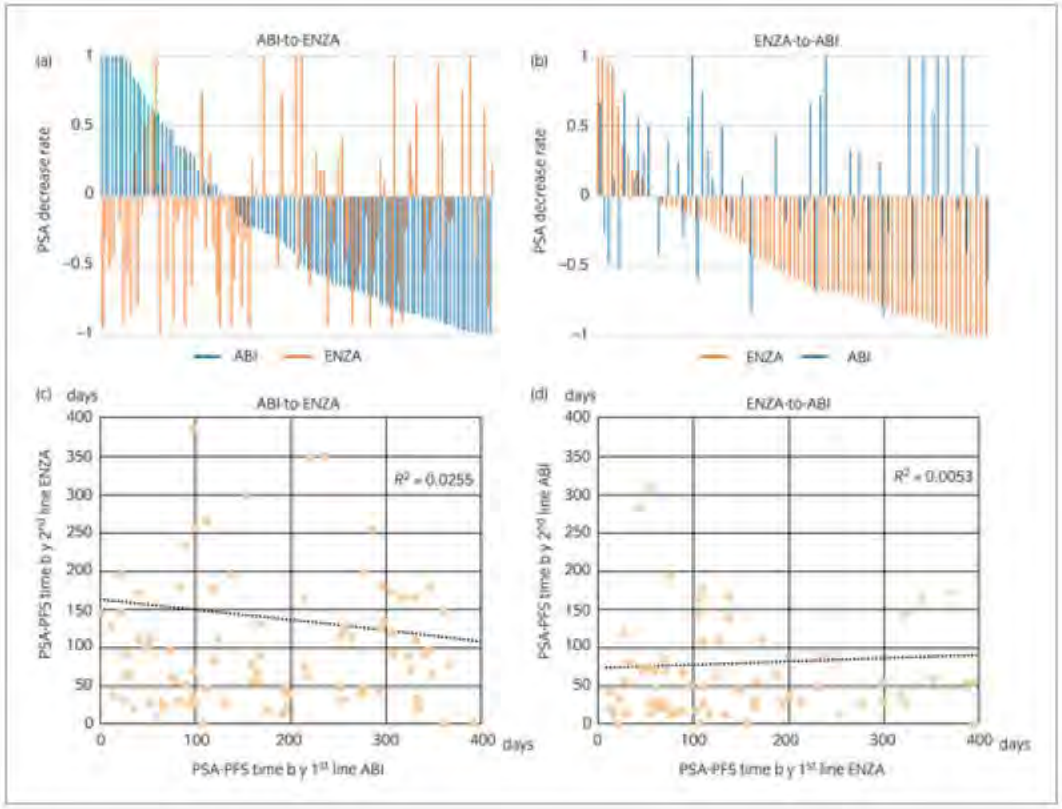

Figure 4

Open in figure viewer | PowerPoint

Best PSA response rate of first- and second-line treatment in (a) the ABI-to-ENZA group and (b) the ENZA-to-ABI group. PSA-PFS time of first- and second-line treatment in (c) the ABI-to-ENZA group and (d) the ENZA-to-ABI group.

Discussion

In the present retrospective multi-institutional study of 352 patients with CRPC treated with sequential ABI-to-ENZA or ENZA-to-ABI in Japan and the USA, we compared the PSA response rates, PSA-PFS and OS outcomes in each sequence in chemotherapy-naïve patients. The efficacy of second-line novel hormonal therapy was attenuated after treatment with previous first-line novel hormonal therapy, as previously described. This finding is consistent with previous observations16, 17 and might represent a manifestation of cross-resistance between these two novel hormonal therapies.[16,17]

We previously reported that the PFS tended to be longer in the ABI-to-ENZA sequence than in the ENZA-to-ABI sequence in a preliminary retrospective study of 81 patients (65 receiving ABI-to-ENZA and 16 receiving ENZA-to-ABI) treated at Johns Hopkins; however, the difference was not statistically significant.18 Notably, ABI was approved first in the USA, and it was generally used first instead of ENZA at Johns Hopkins. In contrast, ENZA was approved first in Japan, and it was generally used initially instead of ABI in Kyoto. In the present multi-institutional study, the number of patients increased from 81 to 352, and the number of men receiving each treatment sequence became more well-balanced (163 in ABI-to-ENZA and 189 in ENZA-to-ABI). Here, the difference in PSA-PFS became statistically significant, and continued to favor the ABI-to-ENZA sequence. The higher PSA response rate and the longer PSA-PFS with ENZA versus ABI as the second-line setting provides one plausible explanation for the difference in the combined PSA-PFS observed in the current analysis. However, the difference in the individual PSA-PFS (ABI *vs* ENZA first-line, ENZA *vs* ABI second-line) was modest and in fact favored ABI as first-line treatment (median 194 *vs* 126 days), as well as ENZA as second-line treatment (91 *vs* 55 days). The combined analysis showed a longer difference of approximately 150 days (455 *vs* 296 days). The difference in PSA-PFS of the first-line treatment might be caused by the differences in baseline characteristics, especially the number of prior anti-androgen treatments. The bigger difference in the combined analysis factor might be caused by the variable reason for stopping first-line therapy (i.e. PSA, radiographic, symptomatic), with many patients staying on therapy beyond PSA progression.

Why is the clinical efficacy of ENZA potentially better than that of ABI in the second-line CRPC scenario? In a study using a prostate cancer xenograft model, expression levels of AR increased by treatment with ABI in the mouse bearing human prostate cancer tumor cells.19 Importantly,

ENZA is known (and was designed) to be effective in CRPC with increased AR expression *in vitro*.[20] This might be one of the mechanisms explaining why ENZA was partially effective for ABI-resistant CRPC patients. In contrast, the AR expression of ENZA-resistant prostate cancer cell lines did not increase consistently, showing that non-AR mediated mechanisms are mainly associated with treatment resistance.[21] These mechanisms of resistance to ENZA could not be overcome by ABI. To further elucidate the mechanisms for the cross-resistance between ABI and ENZA, more basic and clinical research will be required, especially in the context of prospective biomarker studies.

In the present study, there was no correlation between the efficacy of first- and second-line therapy. ABI and ENZA target AR in CRPC through different pathways. Even for the primary resistant patients for first-line treatment, second-line treatment might be one treatment option, especially ENZA after ABI (Fig. 4a,c). In ABI after ENZA, three patients showed a PSA decrease of ≥50% and/or PSA-PFS of longer than 200 days after primary resistance to ENZA (Fig. 4b,d). One patient changed treatment because of toxicities, and two patients because of treatment resistance. However, the present study contains only patients who received second-line AR targeting therapy. Therefore, the patients with very aggressive cancer had been excluded, because the physician selected DTX or cabazitaxel after the first-line AR-targeting therapy. It could not be concluded that second-line AR-targeting therapy was indicated for all the CRPC patients.

There were several limitations of the present study. It was a retrospective analysis that included non-randomized treatment allocation, a lack of appropriate controls, an inability to dictate the subsequent treatments in each cohort, a non-standardized time of data collection between patients, difference in the timing of changing ABI-to-ENZA or ENZA-to-ABI in each patient and the inability to appropriately balance the groups with respect to baseline characteristics, especially the number of prior anti-androgen treatments. However, in the multivariate Cox proportional hazard analyses, the treatment sequence significantly correlated with PSA-PFS. Also, treatment efficacy was evaluated only using PSA progression (not by radiological progression), because the timing of radiological assessments after ABI or ENZA treatment was different among patients as a result of divergent institutional and physician/patient preferences. Furthermore, we did not capture data on treatment-related adverse events or dose-reductions/dose-interruptions, so it was not possible to ascertain to what degree side-effects or medication compliance might have influenced the results. Finally, the lack of available biomarker data, such as hemoglobin, alkaline phosphatase or lactate dehydrogenase, from these patients is another significant shortcoming. Therefore, these results require prospective confirmation before they are used to guide clinical practice.

In conclusion, the present study provides preliminary evidence to suggest superiority of the ABI-to-ENZA sequence (compared with ENZA-to-ABI sequence) with respect to PSA-PFS, but not

OS in unselected patients with CRPC. Ongoing randomized studies evaluating optimal treatment sequencing will definitely answer this question in the near future.

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Conflict of interest

ESA has served as a paid consultant/advisor to Janssen, Johnson & Johnson, Medivation and Astellas; he has also received research funding to his institution from Janssen, Johnson & Johnson, Medivation and Astellas. The other authors declare no conflict of interest.

References

1 Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J. Clin.* 2014; **64**: 9–29.
Wiley Online Library | PubMed | Web of Science® | Google Scholar

2 Ito K. Prostate cancer in Asian men. *Nat. Rev. Urol.* 2014; **11**: 197–212.
Crossref | PubMed | Web of Science® | Google Scholar

3 Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. *Nat. Clin. Pract. Urol.* 2009; **6**: 76–85.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

4 Tannock IF, de Wit R, Berry WR *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* 2004; **351**: 1502–12.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

5 Li Z, Alyamani M, Li J *et al*. Redirecting abiraterone metabolism to fine-tune prostate cancer anti-androgen therapy. *Nature* 2016; **533**: 547–51.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

6 de Bono JS, Logothetis CJ, Molina A *et al*. Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* 2011; **364**: 1995–2005.
Crossref | PubMed | Web of Science® | Google Scholar

7 Ryan CJ, Smith MR, de Bono JS *et al*. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N. Engl. J. Med.* 2013; **368**: 138–48.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

8 Scher HI, Fizazi K, Saad F *et al*. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* 2012; **367**: 1187–97.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

9 Beer TM, Tombal B. Enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* 2014; **371**: 1755–6.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

10 Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. *Eur. Urol.* 2015; **67**: 23–9.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

11 Suzman DL, Luber B, Schweizer MT, Nadal R, Antonarakis ES. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. *Prostate* 2014; **74**: 1278–85.
Wiley Online Library | CAS | PubMed | Web of Science® | Google Scholar

12 Antonarakis ES, Lu C, Wang H *et al*. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N. Engl. J. Med.* 2014; **371**: 1028–38.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

13 Maughan BL, Antonarakis ES. Androgen pathway resistance in prostate cancer and therapeutic implications. *Expert Opin. Pharmacother.* 2015; **16**: 1521–37.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

14 Flaig TW, Potluri RC, Ng Y, Todd MB, Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. *Cancer Med.* 2016; **5**: 182–91.
Wiley Online Library | PubMed | Web of Science® | Google Scholar

15 Scher HI, Halabi S, Tannock I *et al*. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J. Clin. Oncol.* 2008; **26**: 1148–59.
Crossref | PubMed | Web of Science® | Google Scholar

16 Lorente D, Mateo J, Perez-Lopez R, de Bono JS, Attard G. Sequencing of agents in castration-resistant prostate cancer. *Lancet Oncol.* 2015; **16**: e279–92.
Crossref | PubMed | Web of Science® | Google Scholar

17 Lebdai S, Basset V, Branchereau J *et al*. What do we know about treatment sequencing of abiraterone, enzalutamide, and chemotherapy in metastatic castration-resistant prostate cancer? *World J. Urol.* 2016; **34**: 617–24.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

18 Maughan BL, Luber B, Nadal R, Antonarakis ES. Comparing sequencing of abiraterone and enzalutamide in men with metastatic castration-resistant prostate cancer: a retrospective study. *Prostate* 2017; **77**: 33–40.
Wiley Online Library | CAS | PubMed | Web of Science® | Google Scholar

19 Mostaghel EA, Marck BT, Plymate SR *et al*. Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. *Clin. Cancer Res.* 2011; **17**: 5913–25.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

20 Chen CD, Welsbie DS, Tran C *et al*. Molecular determinants of resistance to antiandrogen therapy. *Nat. Med.* 2004; **10**: 33–9.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

21 Kregel S, Chen JL, Tom W *et al*. Acquired resistance to the second-generation androgen receptor antagonist enzalutamide in castration-resistant prostate cancer. *Oncotarget* 2016; **7**: 26259–74.
Crossref | PubMed | Web of Science® | Google Scholar

Citing Literature

Number of times cited according to CrossRef: 8

Kazumasa Komura, Christopher J Sweeney, Teruo Inamoto, Naokazu Ibuki, Haruhito Azuma and Philip W Kantoff, Current treatment strategies for advanced prostate cancer, *International Journal of Urology*, **25**, 3, (220-231), (2017).
Wiley Online Library

Darren M.C. Poon, Kenneth C.W. Wong, T.W. Chan, Kitty Law, Kuen Chan, Eric K.C. Lee, Conrad Lee and Michelle Chan, Survival Outcomes, Prostate-specific Antigen Response, and Tolerance in First and Later Lines of Enzalutamide Treatment for Metastatic Castration-resistant Prostate Cancer: A Real-World Experience in Hong Kong, *Clinical Genitourinary Cancer*, 10.1016/j.clgc.2018.07.008, **16**, 5, (402-412.e1), (2018).
Crossref

Hamid Emamekhoo, Pedro C. Barata, Natasha C. Edwin, Kaitlin M. Woo, Petros Grivas and Jorge A. Garcia, Evaluation of Response to Enzalutamide Consecutively After Abiraterone Acetate/Prednisone Failure in Patients With Metastatic Castration-resistant Prostate Cancer, *Clinical Genitourinary Cancer*, 10.1016/j.clgc.2018.08.002, **16**, 6, (429-436), (2018).
Crossref

Abhimanyu Thakur, Aishwarya Roy, Arijit Ghosh, Mohit Chhabra and Sugato Banerjee, Abiraterone acetate in the treatment of prostate cancer, *Biomedicine & Pharmacotherapy*, 10.1016/j.biopha.2018.02.067, **101**, (211-218), (2018).
Crossref

Nobuaki Matsubara, Yoko Yamada, Ken-ichi Tabata, Takefumi Satoh, Naoto Kamiya, Hiroyoshi Suzuki, Takashi Kawahara, Hiroji Uemura, Akihiro Yano, Satoru Kawakami, Masafumi Otsuka and Satoshi Fukasawa, Abiraterone Followed by Enzalutamide Versus Enzalutamide Followed by Abiraterone in Chemotherapy-naive Patients With Metastatic Castration-resistant Prostate Cancer, *Clinical Genitourinary Cancer*, (2017).
Crossref

Kazutaka Saito and Yasuhisa Fujii, Antitumor Activity and Safety of Enzalutamide After Abiraterone Acetate: Seeking the Optimal Treatment Sequence for Castration-resistant Prostate Cancer Patients, *European Urology*, (2017).
Crossref

Mike Fang, Mary Nakazawa, Emmanuel S. Antonarakis and Chun Li, Efficacy of Abiraterone and Enzalutamide in Pre- and Postdocetaxel Castration-Resistant Prostate Cancer: A Trial-Level Meta-Analysis, *Prostate Cancer*, **2017**, (1), (2017).
Crossref

Koji Mitsuzuka, Editorial Comment to Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant prostate cancer: The Kyoto-Baltimore collaboration, *International Journal of Urology*, **24**, 6, (448-448), (2017).
Wiley Online Library

EXHIBIT AA

WebMD

Early Chemo and Advanced Prostate Cancer Survival

Study found combination with hormone therapy extended life by almost a year

FROM THE WEBMD ARCHIVES

By Dennis Thompson

HealthDay Reporter

THURSDAY, May 14, 2015 (HealthDay News) -- Starting the chemotherapy drug docetaxel at the same time as hormone therapy can improve survival for men with newly diagnosed, advanced prostate cancer, British researchers say.

Currently, chemotherapy is generally given after hormone therapy stops working. But the new study found that when the two therapies were paired at the start of treatment, patients lived an average of 10 months longer.

The combination had even greater benefits for men whose prostate cancer had spread to other parts of their bodies -- known as "metastatic" cancer. These men experienced an average 22-month improvement in their overall survival, the findings showed.

"We hope our findings will encourage doctors to offer docetaxel to men newly diagnosed with metastatic prostate cancer, if they are healthy enough for chemotherapy," said lead author Dr. Nicholas James, director of the Cancer Research Unit at the University of Warwick in Coventry, England.

Since the 1940s, hormone therapy has been the standard treatment for men with advanced prostate cancer. "Essentially we treat men by shutting off the production of male hormones, either surgically or with drugs," James said.

Cancer doctors have followed this tactic because hormone therapy is less toxic and has fewer side effects than chemotherapy, said the president of the American Society of Clinical Oncology, Dr. Peter Yu.

"The bias has been to use hormone therapy until there's no response left, and then at the last moment use chemotherapy," said Yu, who's also the director of cancer research at Palo Alto Medical Foundation in California. He described this as a "self-defeating strategy, because you're using chemotherapy when the disease has evolved to a point where it's much more aggressive."

Findings from the study are scheduled to be presented May 31 at the annual meeting of the American Society of Clinical Oncology in Chicago. Research presented at meetings is generally viewed as preliminary until published in a peer-reviewed journal.

This British-led clinical trial sought to test whether adding chemotherapy up front would help prolong the lives of men with prostate cancer. The study was dubbed STAMPEDE, for Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

Since 2005, researchers have recruited nearly 3,000 prostate cancer patients who'd never had hormone therapy before. About three out of five men in the study had prostate cancer that had spread to other parts of their bodies, while the rest had high-risk, advanced prostate cancer that had not yet spread.

The men entered one of four treatment regimens. They all were given three years of hormone therapy. One group only received the hormone therapy. Another group was given the chemotherapy drug docetaxel in addition to the hormone therapy. The third group got zoledronic acid, a drug used to treat prostate cancer that has spread to bones, along with hormone therapy. The last group got the works -- hormone therapy, docetaxel and zoledronic acid.

In addition, men who were candidates for radiation therapy in any of the groups also received that treatment, according to the study.

After an average follow-up of 42 months, 948 men in the trial had died, the researchers reported.

Men treated with hormone therapy alone lived an average of 67 months. Those treated with docetaxel and hormone therapy ended up surviving an average of 77 months, a relative improvement of 24 percent.

Those with invasive prostate cancer survived an average 65 months when they received docetaxel and hormone therapy together, compared with 43 months for men who received just hormone therapy, the investigators found.

The chemotherapy drug appeared to benefit men by holding their cancer at bay. Docetaxel extended the time to relapse by 38 percent in all patients, the researchers said.

Zoledronic acid didn't have any impact on survival, even when it was combined with both docetaxel and hormone therapy, according to the study.

While the combination of chemotherapy and hormone therapy worked, Yu said doctors will have to take into account the potential for side effects to drastically diminish a patient's quality of life.

Hormone therapy can cause fatigue, anemia, brittle bones, decreased muscle mass and loss of sexual function, while chemotherapy drugs open the body to a host of debilitating side effects, according to Yu and James.

But the researchers noted that the addition of chemotherapy to hormone therapy in this study was well-tolerated. Very few men dropped out due to side effects from the chemotherapy, they added.

"There's no question each of these treatments we introduced has its own possibility for side effects, and so if we're combining therapies there's the potential that you could have a greater negative impact on quality of life," Yu said.

But, he added, "I think we also recognize from other trials that treating the cancer more effectively has a positive benefit in terms of quality of life as well."

Future research will focus on whether this combination therapy also can help men with less aggressive prostate cancer, James said.

WebMD News from HealthDay

Sources

SOURCES: Nicholas James, M.D., Ph.D., director, Cancer Research Unit, University of Warwick, Coventry, England; Peter Yu, M.D., director of cancer research, Palo Alto Medical Foundation, and president, American Society of Clinical Oncology

EXHIBIT BB

Can Xtandi Become the Go-To Prostate Drug?

TODD CAMPBELL, THE MOTLEY FOOL, AOL.COM
Sep 20th 2013 10:48AM

One out of every six men will be diagnosed with prostate cancer.
-- American Cancer Society

At some point, it's likely that all of us will know someone who has been diagnosed with prostate cancer. In my case, it's my stepdad. Prostate cancer has become so common that it's generating big money for drug companies, including **Medivation** and Japanese drug company Astellas, who co-market fast growing drug Xtandi.

A crowded market is getting more crowded

In the past, the dominant treatment for prostate cancer was docetaxel. That drug was formerly sold by **Sanofi**-Aventis as blockbuster Taxotere, a $3 billion a year drug before losing patent protection in 2010.

Today, a number of new prostate cancer drugs have reached the market, including Sanofi's injectible Jevtana, which gained FDA approval in June 2010.

Sanofi developed Jevtana in an attempt to maintain some of Taxotere's post-patent-expiration market share. In phase 3 trials, Sanofi evaluated Jevtana in advanced prostate cancer patients who had seen a worsening during or after treatment with docetaxol. The results were compelling. Jevtana patients saw median overall survival of 15.1 months versus 12.7 months for generic mitoxantrone -- a competing treatment option.

One of the reasons Jevtana's sales slid is Medivation's oral Xtandi, which gained FDA approval as a treatment for metastatic castration resistant prostate cancer last August.

In phase 3 trials, Medivation studied Xtandi in advanced prostate cancer patients who had previously been treated with docetaxol, a common treatment when patients develop a resistance to bicalutamid, a widely used monotherapy for early-stage patients.

Those treated with Xtandi had overall survival of 18.4 months versus just 13.6 months for placebo. As a result, Xtandi is being increasingly prescribed over Jevtana.

Prescription growth pushed Xtandi's Q2 sales up to $82 million, 95% of which were in the United States. International sales should move significantly higher since Canada approved the drug in May and the EU approved the drug in July.

A right-for-everyone drug?

Medivation has an ongoing phase 3 study for Xtandi as a pre-chemo prostate therapy. Preliminary results from that study are expected this year.

If the data is positive, it erases an advantage held by **Johnson & Johnson**'s Zytiga, another recent prostate cancer drug.

Zytiga got approval as a pre-chemo treatment last December and sales have surged, making Zytiga -- with $192 million in second-quarter sales -- one of the top 100 drugs sold in the U.S. Many expect Zytiga sales will continue to grow, potentially reaching $1.8 billion in sales by 2015, according to Decision Resources.

The sales opportunity to strip away Zytiga's market leading market share isn't lost on Medivation. Xtandi already owns 20% of the market for second line treatment, and the company hopes that positive data can slow Zytiga's momentum.

Once data from the phase 3 preliminary data is released, attention will likely focus on overall survival, with an eye toward whether Xtandi extends survival beyond the five months for those

promising early stage prostate cancer treatment born out of the same UCLA research department as Xtandi. It's so promising that Medivation and Astellas sued challenging others ability to commercialize it. So far, Medivation has come up short in proving its case. But, even if Medivation doesn't block J&J's newly acquired ARN-509, it's likely years before patients will have access to it.

Even more interesting than the pre-chemo indication would be success in its ongoing phase 2 trial of Xtandi versus first line treatment bicalutamid. If that study proves successful, Xtandi could elevate into the go-to first line choice for treating prostate cancer. That would likely push Xtandi much closer to blockbuster status.

A big and growing market for Xtandi

Last fall, Citi Investment Research estimated that Xtandi sales would grow to $172 million in 2013 and $390 million in 2014. Six months into this year, Xtandi already had sales of $157 million, suggesting it will significantly exceed the estimate for this year.

According to Decision Resources, drugs like Xtandi and Zytiga will fuel a doubling of prostate cancer spending to $9.1 billion by 2021. Research firm FirstWord estimates the global market for prostate treatment will increase to $7.7 billion in 2017, from $3.5 billion in 2012. The bullish forecasts are in part because the drugs aren't cheap. Zytiga costs $5,500 a month, while Xtandi gets $7,450 a month.

But, the upside is also tied to a bigger global patient pool. While incidence rates have declined in the U.S., there are 238,000 new cases of prostate cancer diagnosed annually. And there were 2.6 million men with a history of prostate cancer in the U.S. alone in 2010. Since six in 10 patients are over 65 when they're diagnosed, a longer living global population likely means more people requiring treatment.

The final take

A rising patient pool is likely to drive to drive overall spending on prostate cancer treatment

Another opportunity in health care investing

Rising health care costs continue to be a hotly debated topic, and even legendary investor Warren Buffett called this trend "the tapeworm that's eating at American competitiveness." To learn more about what's happening to the health care system -- and how to potentially profit from this trend -- click here for free, immediate access.

The article Can Xtandi Become the Go-To Prostate Drug? originally appeared on Fool.com.

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EXHIBIT CC

The New York Times

HEALTH

New Drugs Fight Prostate Cancer, but at High Cost

By ANDREW POLLACK JUNE 27, 2011

A group of new drugs is promising to prolong the lives and relieve the symptoms of men with advanced prostate cancer, but could also add billions of dollars to the nation's medical bills.

In the last 15 months, three new drugs that extended the lives of prostate cancer patients in clinical trials have been approved by the Food and Drug Administration and several other promising medicines are in clinical trials. Before last year, only one drug had been shown to improve survival — docetaxel, which was approved in 2004.

"What a great time it is in prostate cancer," Dr. Daniel J. George of the Duke Cancer Institute proclaimed earlier this month at the annual meeting of the American Society of Clinical Oncology.

And it's a great time for the drug makers, with several drugs competing to fill a niche for longer-term survival. Analysts estimate that some of the new drugs, particularly Dendreon's Provenge and Johnson & Johnson's Zytiga, could reach annual sales of $1 billion or even much more.

check by hormone therapy.

Men with that late-stage cancer had a median survival of about a year and a half using docetaxel. The new drugs each added two to five months to median survival when tested in clinical trials. Doctors say that men taking more than one of the drugs in succession would be expected to live more than two years.

But the price of these drugs has already stirred concerns about the costs of care among patients, providers and insurers. For example, Provenge costs $93,000 for a course of treatment, while Zytiga costs about $5,000 a month. Another of the new drugs, Sanofi's Jevtana, costs about $8,000 every three weeks.

With other pricey drugs on the way, said Joel Sendek, an analyst at Lazard, "We could be talking easily $500,000 per patient or more over the course of therapy, which I don't think the system can afford, especially since 80 percent of the patients are on Medicare."

Medicare has already fired what some analysts interpret as a warning shot over prices, conducting a yearlong inquiry into whether to pay for Provenge. In its final decision, due Thursday, Medicare is expected to pay for the drug when used according to the label.

Medicare officials denied that price was the reason for the review. But some patient advocates and politicians portrayed the review as a step toward rationing.

Private insurers are also paying only if drugs are used according to the label, according to doctors and patient advocates.

"The reality is, there's pushback," said Dr. Oliver Sartor of Tulane University.

Still, for now, one company's price is prompting the next one to follow suit.

"The pricing environment is encouraging and getting better for us," Andrew Kay, the chief executive of Algeta, told securities analysts earlier this month, after announcing that his company's experimental drug had extended median survival

Mr. Kay said he had initially thought that his company, which is based in Norway, would charge about $25,000 for a typical course of treatment with the drug, Alpharadin. But with the rival drug Jevtana costing about $50,000, Algeta and its partner, Bayer, are considering a higher price.

About 218,000 men in the United States get prostate cancer each year and about 32,000 die, according to the American Cancer Society.

In many cases, the cancer is caught before it has spread beyond the prostate gland and can be cured with surgery or radiation therapy.

If the cancer has spread, men usually are given drugs, particularly Abbott Laboratories' Lupron, that suppress the body's production of the hormone testosterone, which can fuel tumor growth.

The new drugs, for now at least, are for use when this hormone-deprivation therapy has stopped working.

"This is a small subset of people with prostate cancer," said Dr. Charles Myers, a prostate cancer specialist in private practice in Charlottesville, Va., who is a survivor of the disease himself. However, he noted, "It's the group of people who are dying."

Provenge was approved in April 2010 for patients whose cancer was late-stage but not yet causing many symptoms.

Once symptoms, mainly bone pain, have appeared, men are likely to receive docetaxel, a generic drug also sold by Sanofi as Taxotere .

Two other new drugs are approved for use only after docetaxel has been tried. One, Sanofi's Jevtana, is a chemotherapy drug in the same class as docetaxel; it was approved in June 2010. The other is Johnson & Johnson's Zytiga, approved this April.

Many patients and doctors are most enthusiastic about Zytiga and Provenge because they are alternatives to chemotherapy, which many men want to avoid

Zytiga is a new form of hormone therapy. While Lupron mainly blocks production of testosterone by the testes, there is still some hormone produced by the adrenal gland or even by the tumor itself. Zytiga, by inhibiting an enzyme called CYP17, clamps down on testosterone production.

Doctors and patients say the new drugs can offer some men a decent quality of life, although they are not free of side effects. For instance, Zytiga, also known as abiraterone, can cause hypertension and liver damage and must be taken with the steroid prednisone.

Many men are likely to try several of the drugs. Mark Maldonado, a retired postal worker in Omaha, said that Jevtana had helped keep his cancer in check without debilitating side effects. But knowing that the drug would eventually stop working, he and his doctor "talked about abiraterone being the next step in our progress through the drugs."

More competition is coming. Takeda Pharmaceutical and Medivation, a San Francisco company, are separately developing other drugs that block testosterone's production or its effects.

Some of the most exciting advances, doctors say, are in the area of fighting the spread of prostate cancer to the bone. Such bone metastases are very common in men with advanced prostate cancer and account for most of the death and disability from the disease.

Cabozantinib, an experimental drug being developed by Exelixis, seems to be able to virtually eradicate bone metastases in some patients, at least as measured by bone scans, something no other drug has done.

Amgen won F.D.A. approval in November for Xgeva, a drug that reduces the risk of fractures and other problems caused by cancer in the bones. The drug can also delay the spread of cancer to the bones, according to the results of a more recent trial.

"It's beyond the individual drugs," he said. "One sees a manual now on how to go forward."

A version of this article appears in print on June 28, 2011, on Page A1 of the New York edition with the headline: New Drugs Fight Prostate Cancer, But at High Cost.

EXHIBIT DD

RETIREMENT WON'T CHANGE WHO HE IS. NEITHER WILL ADVANCED PROSTATE CANCER.

ZYTIGA® is a prescription medication used in combination with prednisone to treat men with metastatic castration-resistant prostate cancer (mCRPC), a type of advanced prostate cancer that is resistant to medical or surgical treatments that lower testosterone and has spread to other parts of the body.

*Estimate is based on sales and use data in the United States from April 2011 to December 2016.

can.'"

Hear patients and their loved ones share their stories about their diagnosis, their treatment, and how they approach each day.

Watch ZYTIGA® Stories →

What are the most common side effects for ZYTIGA®?

Oral, once-daily ZYTIGA® has an established safety profile. Learn more about side effects and important safety information and discuss taking ZYTIGA® with your doctor.

ZYTIGA® may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia), and fluid retention (edema).**

  Tell your healthcare provider if you get any of the following symptoms:

  - Dizziness
  - Fast heartbeats
  - Feel faint or lightheaded
  - Headache
  - Confusion
  - Muscle weakness
  - Pain in your legs
  - Swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.

- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before

- Yellowing of the skin or eyes
- Darkening of the urine
- Severe nausea or vomiting

The most common side effects of ZYTIGA® include:

- Weakness
- Joint swelling or pain
- Swelling in your legs or feet
- Hot flushes
- Diarrhea
- Vomiting
- Cough
- High blood pressure
- Shortness of breath
- Urinary tract infection
- Bruising
- Low red blood cells (anemia) and low blood potassium levels
- High blood sugar levels, high blood cholesterol and triglycerides
- Certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

THESE ARE NOT ALL THE POSSIBLE SIDE EFFECTS OF ZYTIGA®. FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.

How does ZYTIGA® work?

ZYTIGA® works by interrupting the androgen-making process at an important step. ZYTIGA® interrupts androgen production at 3 sources: the testes, the adrenal glands, AND the tumor itself.

ZYTIGA® is different from some medicines that only decrease androgen production in the testes and do not affect the adrenal glands or prostate tumor tissue.

Learn how ZYTIGA® works

What is ZYTIGA® (abiraterone acetate)?

medical (eg, hormonal) or surgical treatments that lower testosterone and has spread to other parts of the body.
*mCRPC is a type of advanced prostate cancer.Learn more about ZYTIGA®

How was ZYTIGA® proven effective?

ZYTIGA® was proven effective in 2 clinical trials - one for men with metastatic castration-resistant prostate cancer (mCRPC) who had not received prior chemotherapy and another for men with mCRPC who received prior chemotherapy containing docetaxel.

See the clinical trial results

WHAT IS ZYTIGA®?

ZYTIGA® (abiraterone acetate) is a prescription medicine that is used along with prednisone. ZYTIGA® is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

Important Safety Information

Who should not take ZYTIGA® (abiraterone acetate)?

Do not take ZYTIGA® if you are pregnant or may become pregnant. ZYTIGA® may harm your unborn baby. Women who are pregnant or who may become pregnant should not touch ZYTIGA® without protection, such as gloves.

ZYTIGA® is not for use in women or children. **Keep ZYTIGA® and all medicines out of the reach of children**.

Before you take ZYTIGA®, tell your healthcare provider if you:

- Have heart problems
- Have liver problems
- Have a history of adrenal problems
- Have a history of pituitary problems
- Have any other medical conditions
- Plan to become pregnant **(See "Who should not take ZYTIGA®?")**
- Are breastfeeding or plan to breastfeed. It is not known if ZYTIGA® passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA® or breastfeed. You should not do both. **(See "Who should not take ZYTIGA®?")**

If you are taking ZYTIGA®:

- Take ZYTIGA® and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA® one time a day. Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA® or prednisone without talking to your healthcare provider first.
- Take ZYTIGA® on an empty stomach. **Do not take ZYTIGA® with food**. Taking ZYTIGA® with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA®.
- Swallow ZYTIGA® tablets whole. Do not crush or chew tablets.
- Take ZYTIGA® tablets with water.
- Your healthcare provider will do blood tests to check for side effects.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA®. If their female partner may become pregnant a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA®. Talk with your healthcare provider if you have any questions about birth control.
- If you miss a dose of ZYTIGA® or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.

ZYTIGA® may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia), and fluid retention (edema).**
  Tell your healthcare provider if you get any of the following symptoms:
  - Dizziness
  - Fast heartbeats
  - Feel faint or lightheaded
  - Headache
  - Confusion
  - Muscle weakness
  - Pain in your legs
  - Swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with

- Darkening of the urine
- Severe nausea or vomiting

The most common side effects of ZYTIGA® include:

- Weakness
- Joint swelling or pain
- Swelling in your legs or feet
- Hot flushes
- Diarrhea
- Vomiting
- Cough
- High blood pressure
- Shortness of breath
- Urinary tract infection
- Bruising
- Low red blood cells (anemia) and low blood potassium levels
- High blood sugar levels, high blood cholesterol and triglycerides
- Certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

THESE ARE NOT ALL THE POSSIBLE SIDE EFFECTS OF ZYTIGA®.
FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ZYTIGA® can interact with other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA®.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.fda.gov/medwatch, or call 1-800-FDA-1088 (1-800-332-1088).

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healthcare professional.

This information is intended for the use of patients and caregivers in the United States and Puerto Rico only. Laws, regulatory requirements, and medical practices for pharmaceutical products vary from country to country. The Prescribing Information included here may not be appropriate for use outside the United States and Puerto Rico.

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Last updated August 2017. 056663-170821

EXHIBIT EE

Watch patients who have taken XTANDI share their experiences

Learn how XTANDI may help >

Find out how to get started on XTANDI >

Get ongoing XTANDI support >

Who is XTANDI for?

XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body. (This is a type of advanced prostate cancer.)

Important Safety Information

Who should not take XTANDI? XTANDI is not for use in women. Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby. It is not known if XTANDI is safe and effective in children.

Before you take XTANDI, tell your healthcare provider if you:

- Have a history of seizures, brain injury, stroke or brain tumors.
- Have any other medical conditions.
- Have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See "Who should not take XTANDI?"
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of

- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a problem involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include weakness or feeling more tired than usual, back pain, decreased appetite, constipation, joint pain, diarrhea, hot flashes, upper respiratory tract infection, swelling in your hands, arms, legs, or feet, shortness of breath, muscle and bone pain, weight loss, headache, high blood pressure, dizziness, and a feeling that you or things around you are moving or spinning (vertigo).

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see the Full Prescribing Information for complete prescribing information.

astellas MEDIVATION

EXHIBIT FF

JEVTANA (cabazitaxel) injection

Do not receive JEVTANA if your white blood cell count is too low, you've had a severe allergic reaction to JEVTANA or other drugs containing polysorbate 80, or have severe liver problems. View Important Safety Information

Why make JEVTANA your next step?

JEVTANA has been proven to help men live longer

JEVTANA is an infusion medicine that was developed specifically to help men with advanced prostate cancer live longer. It is used as a treatment once the cancer has worsened (progressed) following other anti-cancer medicines, including docetaxel.

JEVTANA has been helping men combat advanced prostate cancer since 2010 and is recommended as a treatment following progression on docetaxel by the National Comprehensive Cancer Network (NCCN) based on a high-level of medical evidence.

JEVTANA (cabazitaxel) injection

Do not receive JEVTANA if your white blood cell count is too low, you've had a severe allergic reaction to JEVTANA or other drugs containing polysorbate 80, or have severe liver problems. View Important Safety Information

travels through the body and attacks cells that divide quickly, including cancer cells.

EXTENDS SURVIVAL
JEVTANA may help you to live longer by reducing your risk of death.

SHRINKS TUMORS
JEVTANA may slow the growth of your cancer by shrinking tumors.

WORKS WHEN DOCETAXEL DOESN'T
JEVTANA may prolong your survival and shrink your tumors even if docetaxel is no longer working.

Talk to your healthcare providers to find out if JEVTANA is right for you. START HERE >

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What is JEVTANA?

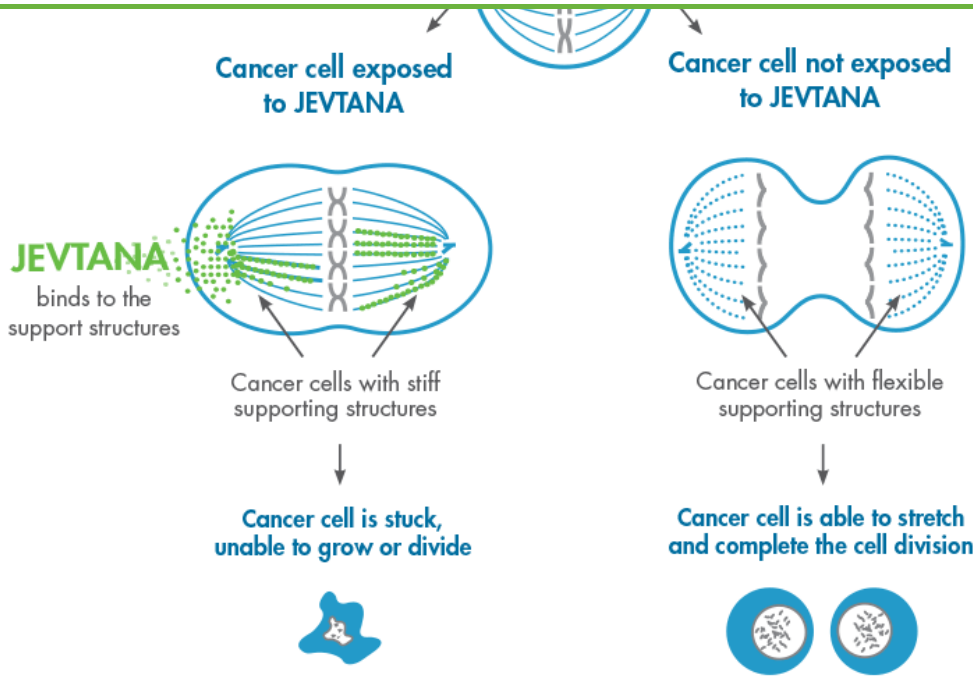
JEVTANA is an infusion medicine used with the steroid medicine prednisone to treat men with prostate cancer that has worsened (progressed) after treatment with other anti-cancer medicines, including docetaxel. JEVTANA has a unique chemical structure different from docetaxel.

How does JEVTANA work?

- JEVTANA attacks rapidly dividing cells, throughout the body, including cancer cells.
- Every cell in your body contains supporting structures, like a miniature scaffolding.

Do not receive JEVTANA if your white blood cell count is too low, you've had a severe allergic reaction to JEVTANA or other drugs containing polysorbate 80, or have severe liver problems. View Important Safety Information

tumor can be highly diverse, some may respond to treatment while others may not.



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How may JEVTANA help?

The effectiveness of JEVTANA was proven in a clinical study of 755 men who:

- Had prostate cancer that spread to other parts of the body
- Were no longer responding to a medical or surgical treatment to lower their testosterone
- Had previously received treatment with docetaxel, a type of anti-cancer infusion medicine

In the clinical study, JEVTANA was shown to improve overall survival in men:

JEVTANA (cabazitaxel) injection

Do not receive JEVTANA if your white blood cell count is too low, you've had a severe allergic reaction to JEVTANA or other drugs containing polysorbate 80, or have severe liver problems. View Important Safety Information

30%

vs mitoxantrone

The number of deaths were 234 (62%) out of 378 patients with JEVTANA and 279 (74%) out of 377 patients with mitoxantrone

15.1 months

vs 12.7 months with mitoxantrone

3x more

14.4% vs 4.4% with mitoxantrone

The median overall survival is the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that half of the patients in a group of patients diagnosed with the disease are still alive. (National Cancer Institute: NCI Dictionary of Cancer Terms. Bethesda, MD: National Cancer Institute, 2013. Available at www.cancer.gov/dictionary. Accessed 11/1/16.)

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What are possible side effects?

Common side effects of JEVTANA include:

- Fever
- Tiredness
- Nausea
- Constipation
- Weakness
- Back pain
- Shortness of breath
- Cough
- Joint pain
- Hair loss
- Stomach (abdominal) pain
- Change in your sense of taste
- Numbness, tingling, burning, or decreased sensation in your hands or feet
- Blood in the urine. Tell your healthcare providers or nurse if you see blood in your urine
- Low red blood cell count (anemia): is common with JEVTANA, but can sometimes also be serious. Your healthcare providers will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness
- Low platelet count: is common with JEVTANA, but can sometimes also be serious. Tell your healthcare providers if you have any unusual bruising or bleeding
- Decreased appetite

These are not all the possible side effects of JEVTANA. For more information, ask your healthcare provider or pharmacist. You may report side effects to FDA at 1-800-FDA-1088.

JEVTANA (cabazitaxel) injection

Do not receive JEVTANA if your white blood cell count is too low, you've had a severe allergic reaction to JEVTANA or other drugs containing polysorbate 80, or have severe liver problems. View Important Safety Information

Is your disease progressing and docetaxel is no longer working?

Talk to your healthcare providers to find out if JEVTANA is right for you.

See page 16 of your brochure for a list of questions to ask your healthcare providers. DOWNLOAD HERE >

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Important Safety Information

What is the most important information I should know about JEVTANA?

JEVTANA may cause serious side effects, including: low white blood cells which can cause you to get serious infections, and may lead to death. People who are 65 years or older may be more likely to have these problems. Your healthcare provider:

- will do blood tests regularly to check your white blood cell counts during your treatment with JEVTANA.
- may lower your dose of JEVTANA, change how often you receive it, or stop JEVTANA until your healthcare provider decides that you have enough white blood cells
- may prescribe a medicine for you called G-CSF, to help prevent complications if your white blood cell count is too low.

Tell your healthcare provider right away if you have any of these symptoms of infection during treatment with JEVTANA: fever (take your temperature often during treatment with JEVTANA), cough, burning on urination, muscle aches.

Also, tell your healthcare provider if you have any diarrhea during the time that your white blood cell count is low. Your healthcare provider may prescribe treatment for you as needed.

Severe allergic reactions can happen within a few minutes after your infusion of JEVTANA starts, especially during the first and second infusions. Your healthcare provider should prescribe medicines before each infusion to help prevent severe allergic reactions.

Tell your healthcare provider or nurse right away if you have any of these symptoms of a severe allergic reaction during or soon after an infusion of JEVTANA: rash or itching, skin redness, feeling dizzy or faint, breathing problems, chest or throat tightness, swelling of face.

JEVTANA can cause severe stomach and intestine (gastrointestinal) problems, which may lead to death. You may need to go to the hospital for treatment.

Vomiting and diarrhea can happen when you receive JEVTANA. Severe vomiting and diarrhea with JEVTANA can lead to loss of too much body fluid (dehydration), or too much of your body salts (electrolytes). Death has happened from having severe diarrhea and losing too much body fluid or body salts with JEVTANA. Your healthcare provider will prescribe medicines to prevent or treat vomiting and diarrhea, as needed with JEVTANA.

Tell your healthcare provider if you have vomiting or diarrhea, and/or if your symptoms get worse or do not get better.

JEVTANA (cabazitaxel) injection

Do not receive JEVTANA if your white blood cell count is too low, you've had a severe allergic reaction to JEVTANA or other drugs containing polysorbate 80, or have severe liver problems. View Important Safety Information

Tell your healthcare provider if you develop these signs or symptoms: swelling of your face or body, decrease in the amount of urine that your body makes each day.

Lung or breathing problems may happen with JEVTANA and may lead to death. People who have lung disease before receiving JEVTANA may have a higher risk for developing lung or breathing problems with JEVTANA treatment. Your healthcare provider will check you for this problem and treat you if needed.

Tell your healthcare provider right away if you develop any new or worsening symptoms, including: trouble breathing, shortness of breath, chest pain, cough, or fever.

Who should not receive JEVTANA Injection?

Do not receive JEVTANA if: your white blood cell (neutrophil count) is too low, you have had a severe allergic reaction to cabazitaxel or other medicines that contain polysorbate 80 (ask your HCP if you are not sure), or you have severe liver problems.

What should I tell my healthcare provider before receiving JEVTANA?

Before receiving JEVTANA, tell your healthcare provider if you: had allergic reactions in the past, have kidney or liver problems, have lung problems, are age 65 or older, have any other medical conditions, are female and

- are pregnant or plan to become pregnant. JEVTANA can harm your unborn baby. Talk to your healthcare provider about the best way for you to prevent pregnancy while you are receiving JEVTANA.
- are breastfeeding or plan to breastfeed. It is not known if JEVTANA passes into your breast milk. You and your healthcare provider should decide if you will take JEVTANA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JEVTANA can interact with many other medicines. Do not take any new medicines without asking your healthcare provider first. Your healthcare provider will tell you if it is safe to take the new medicine with JEVTANA.

What are the possible side effects of JEVTANA?

Common side effects of JEVTANA include:

- Low red blood cell count (anemia) is common with JEVTANA, but can sometimes also be serious. Your healthcare provider will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness.
- Low blood platelet count is common with JEVTANA, but can sometimes also be serious. Tell your healthcare provider if you have any unusual bruising or bleeding.
- fever
- tiredness
- nausea
- constipation
- weakness
- blood in your urine. Tell your healthcare provider or nurse if you see blood in your urine.
- back pain
- numbness, tingling, burning or decreased sensation in your hands or feet
- shortness of breath
- stomach (abdominal) pain
- change in your sense of taste
- cough
- joint pain
- hair loss
- decreased appetite

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of JEVTANA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please click here for full Prescribing Information, including boxed WARNING.

JEVTANA (cabazitaxel) injection

Do not receive JEVTANA if your white blood cell count is too low, you've had a severe allergic reaction to JEVTANA or other drugs containing polysorbate 80, or have severe liver problems. View Important Safety Information

SAUS.CAB.17.03.0717a Last Update: 5/17

EXHIBIT GG

National Acquisition Center (CCST)

Item Details: 57894-0150-12

NATIONAL DRUG CODE (NDC):	57894-0150-12
GENERIC NAME:	ABIRATERONE ACETATE 250MG TAB
TRADE NAME:	ZYTIGA 250MG TAB
VA CLASS:	ANTINEOPLASTIC HORMONES
FSS PRICE:	$9,081.64
PRIME VENDOR (PV):	YES

FSS: 36F79719D0217, J & J Health Care Systems on behalf of Janssen Biotech Inc. details

CONTRACT POINT OF CONTACT:

NAME: Barbara Hawkins
PHONE: 732-562-7322
FAX: 732-562-2121
EMAIL: bhawkin1@its.jnj.com

CORPORATE ADDRESS:

ADDRESS: 800/850 Ridgewood Rd
CITY: Horsham
STATE: PA
ZIPCODE: 19044-3607
SITE:
DUNS: 099091753#

SOCIOECONOMIC INFORMATION: (IF ALL FIELDS BELOW ARE BLANK THEN SIZE IS OTHER THAN SMALL)

SMALL: _
SDB: _
VETERAN OWNED: _
WOMAN OWNED: _
DISABLED VETERAN: _
HUB ZONE: _
8A: _

CONTRACT DATES:

AWARDED: 8/16/2019
EFFECTIVE: 9/1/2019
EXPIRATION: 8/31/2024

NAC CONTRACTING OFFICER (CO):

NAME: Avash Khadka
PHONE: (708)786-5916
EMAIL: Avash.Khadka@va.gov

ORDERING CONTACT:

ADDRESS: 800/850 Ridgewood Rd
CITY: Horsham
STATE: PA
ZIPCODE: 19044-3607
PHONE: 732-562-7322
FAX:
EMAIL: bhawkin1@its.jnj.com

EMERGENCY CONTACT:

NAME:
PHONE:

PAYMENT/DELIVERY INFORMATION:

CREDIT CARD ACCEPTED: No
CREDIT CARD DISCOUNT: None
MINIMUM ORDER: None
DELIVERY TERMS: 7-10 ARO
EXPEDITED DELIVERY: 24 hours. No Charge for Expedited delivery for Government customers.

DISCOUNT INFORMATION:

PROMPT PAYMENT: 2% 30, net 31
QUANTITY DISCOUNT: None

WARRANTY INFORMATION:

DETAILS:

EXHIBIT HH

National Acquisition Center (CCST)

Item Details: 57894-0195-06

NATIONAL DRUG CODE (NDC):	57894-0195-06
GENERIC NAME:	ABIRATERONE ACETATE 500MG TAB
TRADE NAME:	ZYTIGA 500MG TAB
VA CLASS:	ANTINEOPLASTIC HORMONES
FSS PRICE:	$9,519.31
PRICE PER DOSAGE:	$158.66
PRIME VENDOR (PV):	YES

FSS: 36F79719D0217, J & J Health Care Systems on behalf of Janssen Biotech Inc. details

CONTRACT POINT OF CONTACT:

NAME: Barbara Hawkins
PHONE: 732-562-7322
FAX: 732-562-2121
EMAIL: bhawkin1@its.jnj.com

CORPORATE ADDRESS:

ADDRESS: 800/850 Ridgewood Rd
CITY: Horsham
STATE: PA
ZIPCODE: 19044-3607
SITE:
DUNS: 099091753#

SOCIOECONOMIC INFORMATION: (IF ALL FIELDS BELOW ARE BLANK THEN SIZE IS OTHER THAN SMALL)

SMALL: _
SDB: _
VETERAN OWNED: _
WOMAN OWNED: _
DISABLED VETERAN: _
HUB ZONE: _
8A: _

CONTRACT DATES:

AWARDED: 8/16/2019
EFFECTIVE: 9/1/2019
EXPIRATION: 8/31/2024

NAC CONTRACTING OFFICER (CO):

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NAME:
PHONE:

PAYMENT/DELIVERY INFORMATION:

CREDIT CARD ACCEPTED: No
CREDIT CARD DISCOUNT: None
MINIMUM ORDER: None
DELIVERY TERMS: 7-10 ARO
EXPEDITED DELIVERY: 24 hours. No Charge for Expedited delivery for Government customers.

DISCOUNT INFORMATION:

PROMPT PAYMENT: 2% 30, net 31
QUANTITY DISCOUNT: None

WARRANTY INFORMATION:

DETAILS:

EXHIBIT II

Can Zytiga Build on a Historic 2012?

Zytiga enjoyed the most successful oncology drug launch in European history, but it was just the beginning.

Maxx Chatsko
(TMFBlacknGold)
Feb 19, 2013 at 6:33PM
Health Care

Johnson & Johnson (NYSE:JNJ) may offer well-known personal-care products such as Listerine and Neutrogena, but it also boasts an impressive portfolio of market-leading therapeutic compounds. The health-care leader was one of the few to show growth in both worldwide pharmaceutical sales and earnings last year, which grew to $25 billion and $3.86 per share, respectively. It finds itself in an enviable position heading into 2013 as one of the best-positioned companies to tackle the patent cliff head-on.

Even with the recent success, there is no time to rest on laurels in the highly competitive landscape of pharma and biotech. The industry's most successful drugs are under constant pressure from other novel drugs and generics, which are either already on the market or timing their entrance for the moment exclusivity is lost. Luckily, 2012 showed that several new drugs are already shaping up to be critical driving forces in the company's future. Today, we will look at the cancer buster Zytiga.

Don't forget me!

If you were to look at a table of 2011 sales, you would see that Zytiga represented the smallest piece of the pie for Johnson & Johnson. You may think the drug isn't as important as last year's blockbusters Remicade, Stelara, or Velcade. Well, numbers can be misleading.

Zytiga was approved in April 2011 for patients with metastatic castration-resistant prostate cancer, or mCRPC, who have received prior chemotherapy containing docetaxel. The drug narrowly missed the blockbuster threshold in its first full year on the market in 2012 with $961 million in sales. In fact, it was the second most successful oncology drug launch in U.S. history behind only **Roche**'s Avastin and easily the best in European history.

It's difficult to ignore growth like that, especially when Zytiga beat out Remicade for year-over-year sales growth:

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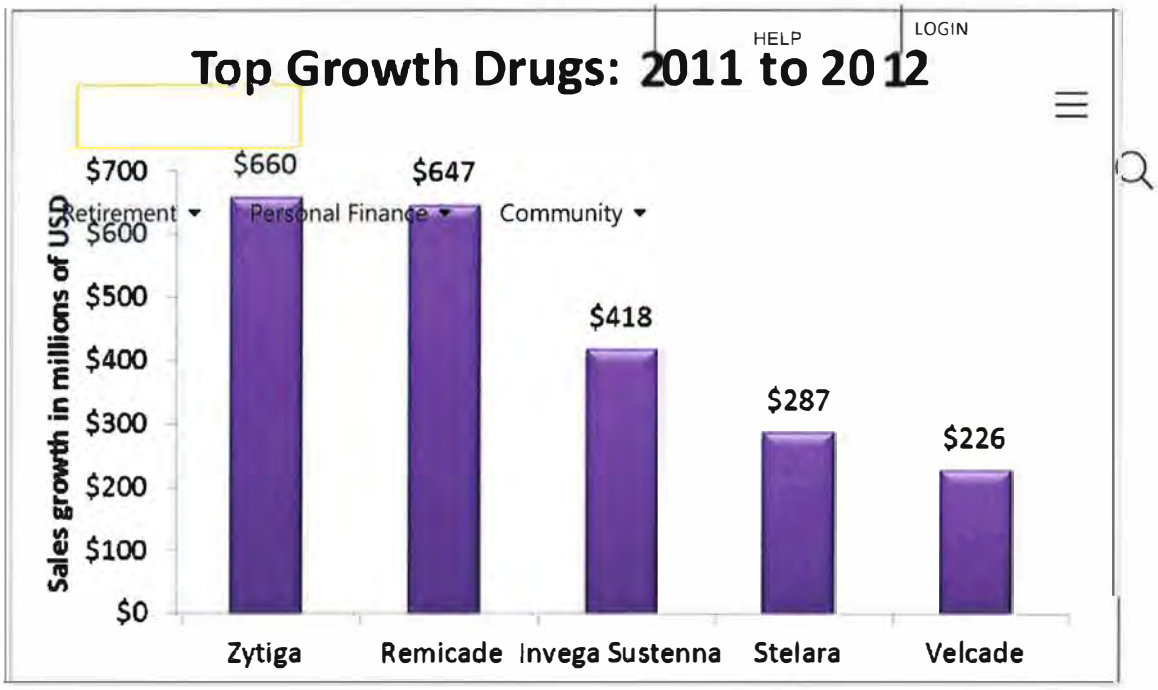


SOURCE: JOHNSON & JOHNSON 2012 EARNINGS

Zytiga had an impressive first year despite being approved in only one fairly limited indication for post-chemotherapy mCRPC, but recent trials give reason to believe it is just the beginning.

It gets better

In early 2012, a trial evaluating Zytiga in patients with mCRPC who had not received chemotheraoy was unblinded after an interim analysis demonstrated clinical benefit in various endpoints and favorable safety profiles -- every company's dream. Even with incomplete data, Zytiga received expanded approval for the new indication in December. It appears that no one at the FDA will be losing sleep over their decision after data released last week showed a near doubling in progression free survival over the control group.

There's always competition

The expanded approval gives a broader range of patients access to the drug, which could mean another stellar year of growth in 2013. Success is great, but you should still watch the competition.

As the first once-daily oral medication for prostate cancer, Zytiga had an immediate advantage over the field of injectable therapies. That is, until **Medivation** (NASDAQ:MDVN) crashed onto the scene -- three months early -- with its oral medication Xtandi for post-chemotherapy use. Medivation's drug improved survival by five months, compared with Zytiga's 4.6 months, but it will also cost much more at $7,450 per month, compared with $5,495 per month for Zytiga. Both drugs are offered at a lower price point than injectables such as **Sanofi**'s (NASDAQ:SNY) Jevtana, which costs $8,242 for three weeks of therapy.

Foolish bottom line

Johnson & Johnson estimates that the overall U.S. prostate cancer market will grow to $3.6 billion in 2016 from just $1.8 billion in 2011. Zytiga's expanded approval opens up a larger slice of the market, while its price advantage over Xtandi should allow it to continue its dominance. The

NEXT ARTICLE ›

current article series on Johnson & Johnson's pharmaceutical segment has offered investors a glimpse into the company's future, but it's only one part of the health care giant's diverse business model. You may be wondering ...

http://www.nytimes.com/2012/09/01/business/fda-approves-prostate-cancer-drug.html?_r=0

Zytiga and Jevtana pricing:

See the footnote for the graph in the attached image.

EXHIBIT JJ

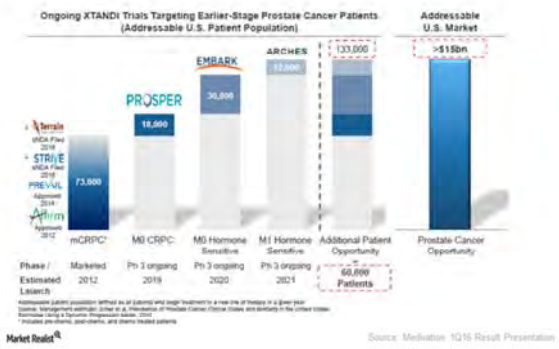
Analyzing Medivation's Growth Opportunity with Xtandi

Jillian Dabney
Market Realist May 12, 2016

Why Is Medivation a Good Acquisition Target?

Medivation's growth opportunity with Xtandi

Xtandi is Medivation's (MDVN) key drug. Currently, it's approved for mCRPC (metastatic castration-resistant prostate cancer). Additional studies will expand the population base for the drug from the current addressable 73,000 patients in the US to 133,000 patients in the country. It presents an opportunity for the drug to serve another 60,000 patients.



NHT market growth

Xtandi is the preferred NHT (novel hormone therapy). The NHT market consists of Xtandi and Zytiga. The sales grew from $1 billion in 2012 to $4.1 billion in 2015. Xtandi competes directly with Johnson & Johnson's (JNJ) Zytiga. It surpassed the drug in terms of sales. With the continued growth of the overall NHT market and Xtandi's increasing market share along with additional indications, the drug would have an addressable market of over $15 billion in sales.

Zytiga and Xtandi dominate the NHT market

Excluding Xtandi and Zytiga, there are three other drugs with proven benefits in the prostate cancer space. These drugs are Dendreon's (DNDNQ) Provenge, Bayer Healthcare's Xofigo, and Sanofi's (SNY) Jevtana. However, the NHT market is dominated by Xtandi and Zytiga. Only these two drugs have "demonstrated both overall survival and progression-free survival benefits in a broad label covering both pre-chemo and post-chemo patients." Xtandi's upstream label expansion is comparing the drug with AstraZeneca's (AZN) Casodex.

Increasing duration of therapy

Another driver behind the drug's success is its increasing duration of therapy. Medivation expects Xtandi's duration of therapy to be around 15.3 months in the mCRPC space.

Read Medivation Sees Growth in Xtandi: A Major Oncology Drug and Could Medivation's Xtandi Become a Major Urology Drug? to learn about more opportunities for the drug.

One of the funds that hold assets such as Medivation in its portfolio is the iShares Nasdaq Biotechnology ETF (IBB). It offers 1.9% weight to Medivation's stock.

EXHIBIT KK

EVERYDAY UROLOGY™

ONCOLOGY INSIGHTS – A UROTODAY® PUBLICATION

VOLUME 1, ISSUE 4

First of its Kind: A Core Curriculum for Urologic Nursing

DIANE NEWMAN, DNP, ANP-BC, FAAN, BCB-PMD

mCRPC Treatment: The Right Treatment for the Right Patient at the Right Time

CHARLES J. RYAN, MD

The Multidisciplinary Cancer Clinic

ALICIA K. MORGANS, MD, MPH

Spotlight: SUO 2016 Conference Highlights

PART TWO

mCRPC Treatment: The Right Treatment for the Right Patient at the Right Time

By Charles J. Ryan, MD

CHARLES J RYAN, MD is a prominent researcher and leading clinician in the treatment of prostate and other urologic cancers. Dr. Ryan was one of the leading researchers for the COU-AA-302 clinical trial, which led to the FDA approval of abiraterone acetate plus prednisone as the first oral therapy for treatment of chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC). Dr. Ryan is Professor of Clinical Medicine and Urology and Thomas Perkins Distinguished Professor in Cancer Research, Program Leader, Genitourinary Medical Oncology at the University of California-San Francisco Helen Diller Family Comprehensive Cancer Center in San Francisco, California. In the following article, he reflects on treatment considerations in using the newest treatments for mCRPC, including patient characteristics and mechanisms of resistance.

Metastatic castration-resistant prostate cancer (mCRPC) presents with a wide spectrum of symptoms with varying effects on patient quality of life. It is estimated that more than 90% of patients with metastatic castrate resistant prostate cancer (mCRPC) develop bone metastases that result in a significant increase in the risk of morbidity.[1]

The extent of bone involvement in mCRPC has also been found to be associated with patient survival. While most patients are clinically asymptomatic, those with symptoms may experience either pain and/or skeletal-related events (SREs). Patients can have low-volume disease with very few symptoms and a good quality of life, but there are also patients who present with high-volume disease that causes significant and painful symptoms. So, the aim of therapy in patients with mCRPC is to match the appropriate strength therapy to the appropriate level of patient symptoms and disease burden.

In patients with mCRPC with low disease burden and few symptoms—or patients with slow-moving disease without visceral metastases and a fairly good prognosis—it's reasonable to consider using sipuleucel-T immunotherapy as an initial therapy. In studies with sipuleucel-T, patients with a low disease burden who received the immunotherapy showed improved survival rates compared to patients who received placebo. As well as its survival benefit, sipuleucel-T's unique mechanism of action makes it a good choice for some mCRPC patients with good performance status[2].

For patients who have a good prognosis, it can also be wise to wait 2 to 3 months before starting therapy to get a sense of the pace of their disease. As long as patients remain in a good prognostic category, asymptomatic, and with less aggressive tumor biomarkers—such as alkaline phosphatase and lactate dehydrogenase—waiting 2 to 3 months is often not problematic. Once the clinician obtains additional information about the pace of the patient's cancer progression over several months, it becomes easier to choose the most appropriate therapy.

Abiraterone and enzalutamide are novel androgen receptor oral therapies that provide comparable survival benefits in patients with mCRPC. In choosing whether to treat a patient with mCRPC with abiraterone and enzalutamide, a number of patient characteristics should be considered. In younger, healthier patients, either drug is fine. However, enzalutamide tends to have more central nervous system toxicity, so it is best to avoid this drug in older or frail patients, or in patients with a history of falls, because falls are a risk with enzalutamide. In the PREVAIL study, patients on enzalutamide had a 12% risk of falls vs. a 6% risk of falls for patients on placebo[3]. Other agents may be more appropriate in patients with baseline symptoms of fatigue, or in patients who are affected by confusion or gait imbalance.

In addition, seizures are a known side effect of higher doses of enzalutamide. In the two major clinical trials on enzalutamide—AFFIRM and PREVAIL—seizures were fairly rare, but this therapy should be avoided in patients with a history of seizures[3,4].

For patients with mild baseline pain, abiraterone acetate plus prednisone therapy may be preferable instead. Since abiraterone is given with low-dose prednisone, patients may derive a significant treatment effect from taking the steroid. Approximately 25% of patients who received prednisone alone in the COU-AA-302 study showed a 50% or greater decline in PSA, and patients who experienced this large a decline in PSA survived longer than patients who did not[4]. The steroid use in abiraterone acetate plus prednisone may also favor use of this treatment in older, frailer patients, who may already have signs of mild adrenal insufficiency[5,6].

At the same time, abiraterone can cause fluid retention, and so it should be avoided in patients with a history of heart failure. If a patient has diabetes or renal failure, enzalutamide should also be strongly considered over abiraterone, since abiraterone can have mineralocorticoid-related or cardiotoxic effects. In the COU-AA-302 study, adverse events due to cardiac disorders occurred in 19% of the patients in the abiraterone-prednisone treatment group vs. 16% of patients in the prednisone-alone group. Hypertension was also more common in the

abiraterone-prednisone treatment group (22% vs. 13%), as was fluid retention and edema (28% vs. 24%) and hypokalemia (17% vs. 13%)[5].

The patient's age should not be the only factor one should weigh in choosing whether to treat a patient with enzalutamide or abiraterone. In the COU-AA-302 study, the magnitude of benefit of abiraterone-prednisone therapy was preserved in elderly men 75 years of age or older. The COU-AA-302 trial data showed that abiraterone plus prednisone did not induce harm, and conferred significant benefit in overall survival rates and radiographic progression-free survival rates in elderly men[2]. In contrast, chemotherapy in elderly patients with prostate cancer has the potential to induce harm, and many elderly men cannot undergo chemotherapy[5,6,7].

In the COU-AA-302 study, elderly men did have increased rates of liver toxicity and cardiac events, however. These findings reflect the fact that elderly men are generally more frail; thus, the fluid retention syndrome that abiraterone causes can negatively affect older men with less cardiac reserve. Elderly men also tend to take more medications and have more comorbid illnesses that can adversely affect liver toxicity[5,6].

Still, choosing between enzalutamide and abiraterone can be challenging, even for clinicians with considerable expertise in using these medications. It's unlikely that a randomized clinical trial comparing these two medications will be performed, due to the impracticality of such an effort. Yet, patient-centered comparative effectiveness trials would be possible. Such studies could focus on the quality of life benefits, patient-reported outcomes, and patient-reported adverse events with the use of these medications[8].

To complete these patient-centered outcome studies, researchers could use validated tools such as the PRO-CTCAE, a patient-reported outcome measure developed to evaluate symptom toxicity in patients on cancer clinical trials, and many of the validated quality-of-life measure now available. As a result of such research, clinicians would be able to identify patients who are more likely to benefit or experience side effects from treatments such as abiraterone and enzalutamide therapy.8

One of the major challenges we face in treatment of mCRPC is that resistance to abiraterone and enzalutamide typically develops after 11 to 18 months of beginning therapy. Although many ''responders'' to these drugs show an impressive decline in PSA, along with radiographic disease control, other patients who respond present with a slowly rising PSA. Thus, rising PSA should not be the sole criteria used to decide whether to discontinue one of these medications. Instead, radiographic disease progression, clinical deterioration, and adverse events should be considered together in making decisions about stopping or switching treatments. *(See Figure 1)*

In patients who are on abiraterone or enzalutamide therapy, and develop resistance but do not have significant symptoms,

THE PRO-CTCAE MEASUREMENT SYSTEM

The NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a new patient-reported outcome measurement system developed to characterize the frequency, severity and interference of 78 symptomatic treatment toxicities. These include symptomatic toxicities such as pain, fatigue, nausea, and cutaneous side effects such as rash and hand-foot syndrome, all toxicities that can be meaningfully reported from the patient perspective.

The PRO-CTCAE measurement system consists of an item library of adverse symptoms, and a prototype electronic platform with a variety of features designed to promote integration of the PRO-CTCAE measurement system into clinical trials workflow. The system allows for data collection via the web, a hand-held computer, or an interactive voice-response system, and includes features that allow for customized PRO-CTCAE questionnaires, tailoring the schedule for data collection, as well as patient reminders and clinician alerts for severe symptoms.

Each of the 78 symptom terms included in the PRO-CTCAE item library is assessed relative to one or more distinct attributes, including presence/absence, frequency, severity, and/or interference with usual or daily activities. Responses are provided on a 5-point Likert scale. The standard PRO-CTCAE recall period is "the past 7 days."

PRO-CTCAE is intended to enhance the quality of adverse event data reporting in clinical trials, provide data that complements and extends the information provided by clinician reporting using CTCAE, represent the patient perspective of the experience of symptomatic adverse events, and improve detection of potentially serious adverse events.

Patient-reported Outcomes Version of the Common Terminology Criteria for Adverse Events PRO-CTCAE™) Item Library (Version 1.0)

ATTRIBUTES

F: Frequency

S: Severity

I: Interference

P: Presence/Absence/Amount

ORAL	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

GASTROINTESTINAL	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

RESPIRATORY	
Shortness of breath	SI
Cough	SI
Wheezing	S
Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

NEUROLOGICAL	
Numbness & tingling	SI
Dizziness	SI

CUTANEOUS	
Rash	P
Skin dryness	S
Acne	S
Hair loss	P
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

VISUAL/PERCEPTUAL	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

ATTENTION/MEMORY	
Concentration	SI
Memory	SI
PAIN	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

SLEEP/WAKE	
Insomnia	SI
Fatigue	SI

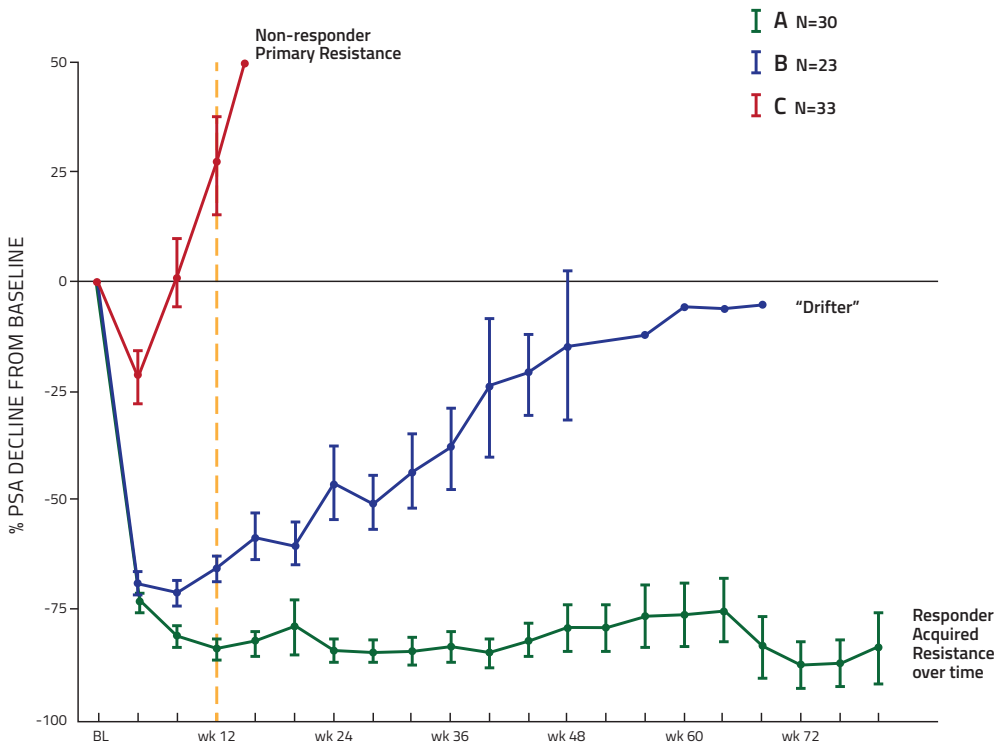
MOOD	
Anxious	FSI
Discouraged	FSI
Sad	FSI

GYNECOLOGIC/URINARY	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	P
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	PI
Change in usual urine color	P
Urinary incontinence	FI

SEXUAL	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

MISCELLANEOUS	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

Figure 1: PSA Response to AR-targeted Therapy



A total of 3 consecutive PSA declines following treatment (A) is associated with prolonged radiographic progression-free survival (RPFS) (median not reached) relative to no sequential declines (B and C) median 23 weeks.

Urologic Oncology: Seminars and Original Investigations 2016 34, 340-347DOI: (10.1016/j.urolonc.2016.05.002)

it's often possible to switch the patient to another of these androgen-receptor targeted drugs. The clinician should keep in mind, however, that retrospective analyses suggest that the second agent is likely to have a more modest degree of activity in patients who do not respond to their first treatment with enzalutamide or abiraterone. As yet, there are few safety concerns with sequential treatment.

Studies are also evaluating these agents in combination, in the hope of obtaining a response rate that is superior to that achieved with abiraterone or enzalutamide alone. The ALLIANCE phase III clinical trial is currently testing this approach in patients who have not had prior taxane-based chemotherapy or treatment with enzalutamide or abiraterone. Yet, since data from this trial will not be available for another two years, combining abiraterone and enzalutamide is not currently recommended in clinical practice.

Recently, we were informed that a Phase 4 clinical trial (PLATO) investigating longer-term use of enzalutamide as a combination treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) did not reach its primary goal of improved progression-free survival. The trial is concluding, but data will continue to be evaluated, according to Pfizer and Astellas Pharma. Top-line results failed to show that continued treatment with enzalutamide in combination with the chemotherapy, abiraterone acetate and prednisone, improved progression-free survival (PFS) in chemotherapy-naive mCRPC patients whose PSA levels had progressed despite previous enzalutamide therapy[9].

The trial is a double-blind, placebo-controlled study, designed to assess the safety and efficacy of continued treatment with enzalutamide plus abiraterone acetate and prednisone following confirmed PSA progression. The study enrolled 509 patients with mCRPC who had never received chemotherapy treatment before, and was divided into two parts. In part one, patients received enzalutamide (160 mg/day) until an increase in their PSA levels was confirmed. In the second part of the trial, patients were randomly assigned to either continue enzalutamide treatment, now combined with abiraterone acetate (1,000 mg/day orally) and prednisone (5 mg administered orally twice daily), or begin treatment with placebo plus abiraterone acetate and prednisone. Its primary goal was progression-free survival, defined by either radiographic progression, unequivocal clinical progression, or death[9].

Patients, who develop symptomatic disease and skeletal metastases while being treated with or following treatment of enzalutamide or abiraterone, should be considered for treatment with radium-223. Radium-223 has been shown to significantly delay the development of symptomatic skeletal events. More importantly, radium-223 is a life-prolongation therapy, as shown in the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) Phase III trial, which demonstrated a statistically significant improvement in overall survival for the radium-223 treatment arm[10].

In this trial of 921 patients who had not received or could not receive docetaxel, radium-223 was compared to placebo. In the trial, patients who received six injections of radium-223 had

a median survival rate of 14.9 months vs. 11.3 months in patients receiving placebo (HR=.70, P <0.0001.) In addition, the median time to the first symptomatic skeletal event was 15.6 months in the radium-223 group vs. 9.8 months in the placebo group (HR=.66, P <0.001)[10].

Radium-223 is approved as a course of therapy consisting of 6 cycles. It is not approved for any additional cycles, although this is being studied. Future trials may show that additional cycles or even higher dosages may be of further benefit. Ongoing studies are evaluating additional combination strategies. The only concomitant agents that are contraindicated in the labeled approval for radium-223 are taxane-based chemotherapies.

In addition to investigating new treatments, researchers have begun to identify mechanisms of resistance to these treatments. These mechanisms of resistance are genetic mutations that affect androgen receptors or are related to DNA repair, and affect treatment outcomes. Recent genomic analyses have revealed that somatic inactivation or germline mutations in genes such as BRCA1, BRCA2, CKD12, and ATM occur in as many as 25% of advanced prostate cancers[10].

PARP inhibitors such as olaparib exploit defective DNA repair in BRCA1/BRCA2 tumors, including prostate cancer tumors. In the TOPARP study, a phase II trial of olaparib in patients with advanced CRPC, olaparib induced responses in tumors with mutations in other DNA repair genes, including ATM and CHEK2. According to recent research, platinum-based chemotherapy is also selective against DNA repair deficiencies[11].

As we move into an era of molecularly targeted therapies, researchers and clinicians need to be mindful of the fact that empiric drug choices will not always be the right choice for every patient. Instead, we may need to perform more genomic sequencing on tumors to see if they contain mutations that can be addressed with a PARP inhibitor or platinum-based chemotherapy. In the near future, we will also be doing androgen-receptor sequencing to determine whether a patient could be resistant to a given androgen receptor-targeted therapy. Thus, we might be able to do a biomarker genomic analysis that could tell us whether a patient will respond to abiraterone, and if not, then we would avoid using this medication.

We are already moving into this era with a major effort by the Stand Up to Cancer Prostate Dream Team 2 (SU2C-PCF), which is exploring mechanisms of resistance to prostate cancer hormonal therapies. For instance, the Stand Up to Cancer Prostate Dream Team is obtaining biopsies and genomic analyses from more than 300 patients with abiraterone-resistant disease. The Dream Team hopes to find the mechanisms of resistance as well as the histological changes that can occur in mCRPC disease as it evolves. From there, the researchers will delve into the prognostic and therapeutic implications for these histological changes. So, a DNA repair defect, for example, might push clinicians toward using a PARP inhibitor or platinum-based chemotherapy that may be selective against certain mutations.

Treatment changes for mCRPC is advancing at a rapid pace. A generation ago, many prostate cancer clinicians would not even begin therapy until after a patient had developed painful symptoms. We now know that this is unacceptable. It's crucial not to withhold a life-saving, disease-controlling therapy until a patient begins to experience painful symptoms.

As we gain additional understanding in the treatment of mCRPC, it's worthwhile for clinicians and patients to ask questions about whether genomic tissue analyses would be beneficial. Through such analyses, clinicians will gain important understanding into the optimal management of patients with mCRPC. The challenge for clinicians in the community, of course, is to obtain the resources for performing tissue analyses. Yet, this effort should not be relegated just to research institutions. It's important for community clinics and clinicians to perform genomic analyses, so that these analyses become part of the standard management of prostate cancer.

When treating bone metastases in CRPC, it is crucial to understand the dynamic nature of the disease, and know that the site of prostate cancer evolves as do the patient's needs. Treatment approaches need to focus on treating the metastases. Clinical interventions in bone metastatic disease can significantly impact outcomes, including survival, skeletal-related events and patient quality of life.

In this article, I have touched on many treatment strategies and clinical approaches—some of which are still being developed. We must be vigilant to accurately assess patients' disease burden, their symptomatology and quality of life. The goal should then be to target treatments to the right patients at the right time, and base these treatment decisions on patients' disease burden, symptoms and characteristics. ■

1. Siegel R, Naishadham D, and Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012; 62 (1): 10–29.

2. Kantoff PW, Higano CS, Shore ND, et al.; the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363: 411-422.

3. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014; 371 (5): 424-33.

4. Fizazi K, Sher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain and quality of life in men with castration-resistant cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol. 2014; 15 (10): 1147-56.

5. Ryan CJ, Smith MR, Fizazi K, et al; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015; 16 (2): 152-60.

6. Smith MR, Rathkopf DE, Mulders PF, et al. Efficacy and safety of abiraterone acetate in elderly (≥75 years) chemotherapy-naïve patients with metastatic castration-resistant prostate cancer. J Urol. 2015;194(5):1277-1284.

7. Dhawan M, Ryan CJ. Utility of novel androgen receptor therapies in the real world: A nuanced approach. Urol Oncol. 2016; 34 (8): 340-347.

8. Kim W, Ryan CJ. Use of androgen receptor signaling-targeted therapies in chemotherapy-naïve metastatic castration-resistant prostate cancer: A call for patient-centered studies. J Comp Eff Res. 2016;5(1)5-7.

9. Pfizer and Astellas announce top-line results from Phase 4 PLATO trial of XTANDI (enzalutamide) capsules in patients with metastatic castration-resistant prostate Cancer. Business Wire. December 14, 2016. http://press.pfizer.com/press-release/pfizer-and-astellas-announce-top-line-results-phase-4-plato-trial-xtandi-enzalutamide-

10. Parker C, Nilsson S, Heinrich D, et al. Updated analysis of the phase III, double-blind, randomized multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). J Clin Oncol. 2012; 30 (18 Suppl): Abstract LBA 4512.

11. Dhawan M, Ryan CJ, Ashworth A. DNA repair deficiency is common in advanced prostate cancer: New therapeutic opportunities. Oncologist. 2016;21(8):940-945.

EXHIBIT LL

May 17, 2017

New Zytiga Tablet Strength Available

Da Hee Han, PharmD

Zytiga is also available as 250mg strength uncoated tablets in 120-count bottles

Zytiga (abiraterone acetate; Janssen Biotech) is available in a new 500 mg strength tablet for use in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer. The new formulation was approved by the Food and Drug Administration (FDA) on April 17, 2017.

The drug labeling has been updated with dosage and administration information to reflect the new tablet strength. Zytiga tablets should be swallowed whole with water; they should not be crushed or chewed.

Zytiga, a CYP17 inhibitor, is converted to abiraterone which inhibits an enzyme expressed on testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Androgen sensitive prostatic carcinoma responds to treatment that lowers androgen levels. Zytiga was shown to lower serum testosterone and other androgens in patients enrolled in a Phase 3 placebo-controlled trial.

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PROSTATE AND OTHER MALE CANCERS

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May 17, 2017

Copanlisib Granted Priority Review for Follicular Lymphoma

Steve Duffy

Bayer plans to request Accelerated Approval for copanlisib

The New Drug Application (NDA) f or copanlisib (Bayer) has been gran ted Priority Review by the Food an d Drug Administration (FDA). Copa nlisib is an investigational treatmen t for patients with relapsed or refra ctory follicular lymphoma who hav e received at least two prior treatments.

Copanlisib is a pan-Class I phosphatidylinositol-3-kinase (PI3K) inhibit or. The NDA submission was based on the Phase 2 trial, 'Chronos-1' wh ich included 141 patients with indolent non-Hodgkin's lymphoma (iNH L). The primary endpoint of the study was objective tumor response ra te, with duration of response, overall survival, progression-free surviva l, quality of life, and safety serving as secondary endpoints. The full findi

ngs were presented at the American Association for Cancer Research's Annual Meeting.

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Bayer is planning to request Accelerated Approval for copanlisib. The company is currently enrolling patients for two Phase 3 trials (Chronos-3 and Chronos-4) to further investigate the efficacy and safety of copanlisib.

Orphan designation has also been granted to copanlisib for the treatment of splenic, nodal, and extranoldal subtypes of marginal zone lymphoma.

For more information visit chronostrials.com.

TOPICS: HEAD AND NECK CANCER | ONCOLOGY

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EXHIBIT MM

MEDICAL NEWS TODAY

Xtandi (Enzalutamide) Approved For Late Stage Prostate Cancer, FDA

By Christian Nordqvist | Published Monday 3 September 2012

Xtandi (enzalutamide) has been approved for men with metastatic castration-resistant prostate cancer that has recurred or spread, regardless of whether patients received medical or surgical therapy to reduce testosterone levels, the US Food and Drug Administration (FDA) announced. Enzalutamide has been approved to be administered alongside docetaxel, another cancer medication.

The FDA reviewed Xtandi under its Priority Review Program, which allows medications to be reviewed within just six months. This type of accelerated program is reserved for drugs that have the potential to offer major treatment advances, or medications for which no proper therapy exists. According to the FDA in an online communiqué "Xtandi received FDA approval three months ahead of the product's prescription drug user fee goal date of Nov. 22, 2012".

Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, FDA, said:

> **"The need for additional treatment options for advanced prostate cancer continues to be important for patients. Xtandi is the latest treatment for this disease to demonstrate its ability to extend a patient's life."**

FDA scientists evaluated Xtandi's efficacy and safety by assessing data from a clinical trial involving 1,199 men with metastatic castration-resistant prostate cancer who had previously received docetaxel. The study's primary endpoint was to measure how long each patient survived (overall survival) - the patients had been randomly selected to receive either Xtandi or a dummy drug (placebo).

The trial showed that those in the Xtandi group survived for an average of 18.4 months, compared to 13.6 months in the placebo group.

Side effects - reported side-effects linked to Xtandi therapy included back pain, headache, upper respiratory infections, hypertension, anxiety, tingling, blood in urine, lower respiratory infections, musculoskeletal pain, tissue swelling, hot flushes, joint pain, diarrhea, fatigue, and weakness.

Approximately 1% of patients on Xtandi had at least one seizure; they were immediately taken off the drug.

The clinical trial had no patients with a history of seizure, stroke, brain metastasis, those on medications which may increase seizure risk, a temporary drop in blood supply to the brain, or any underlying brain injury with loss of consciousness. The FDA said that Xtandi's safety with these patients is unknown.

Xtandi will be manufactured and sold by two companies, Astellas Pharma US Inc., and Medivation Inc.

Charles Sawyers and Michael Jung discovered enzalutamide, which was developed by Medivation Inc. According the company, the drug reported up to an 89% decrease in prostate specific antigen serum levels within a month of treatment in 3 clinical trials. Preliminary clinical studies also indicate that enzalutamide slows down breast cancer cell growth.

The two companies say Xtandi should be available to patients in the USA in mid-September 2012. Medivation says Xtandi has also been submitted for review to EMA (the European Medicines Agency).

David Hung, M.D., co-founder, president and CEO of Medivation, Inc., said:

"Today's approval marks a significant accomplishment for Medivation. We are proud to be in a position to offer a new treatment, XTANDI, for this patient population for which there is a significant unmet medical need. I would like to extend my thanks to the patients, physicians, and their study teams who participated in the clinical trials, and to our employees, and those of our partner Astellas, who have been instrumental in helping us reach this important milestone."

Howard I. Scher, M.D., chief, Genitourinary Oncology Service, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, and co-leader of one of the Xtandi pivotal studies, called "AFFRIM", said that "Enzalutamide provides an exciting new option for physicians that can prolong the lives of patients with metastatic prostate cancer who have received chemotherapy. It is extremely gratifying to have led the clinical trial of enzalutamide, having followed the development of this drug from its early inception in the laboratory to the clinic."

Stephen Eck, M.D., Ph.D., Vice President of Medical Oncology, Astellas Pharma Global Development, said:

"We believe Xtandi has the potential to play an important role in the treatment of advanced prostate cancer. We're eager to work with Medivation to make this much-needed new treatment available to medical professionals and patients in September."

Xtandi, an androgen receptor inhibitor, is taken orally, once a day, in four 40mg capsules (160 mg per day). It can be taken during or before meals and does not require concomitant prednisone. 48% of patients given Xtandi in the phase 3 trial were treated with glucocorticoids. The FDA requires that Medivation and Astellas carry out an open-label safety study in high-risk of seizures patients. The companies say the results from this study should be available in 2019.

Written by Christian Nordqvist

References

"U.S. FDA Approves XTANDI(R) (enzalutamide) After Priority Review for Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel"
Medivation, Inc.

"FDA approves new treatment for a type of late stage prostate cancer "
FDA

Additional information

Citations

EXHIBIT NN

Novartis already sells Fingolimod 0.5mg capsules under the brand name Gilenya in the US market. Photo: Pradeep Gaur/Mint

Natco Pharma files new drug applications with USFDA

1 min read . Updated: 10 Feb 2015, 06:20 PM IST

PTI

The company has filed applications for Fingolimod and Cabazitaxel, used to fight nervous system diseases and cancer

Topics

Natco | Novartis | USFDA | generic drugs | drug applications | cancer | sclerosis | Pharma

New Delhi: Natco Pharma Ltd has filed new product applications with the US health regulator for generic version of drugs used in the treatment of nervous system disease and cancer.

The company has filed Abbreviated New Drug Applications (ANDAs) for Fingolimod, 0.5 mg capsules and Cabazitaxel, 60mg/1.5ml injection, with the US Food and Drug Administration (USFDA), through its respective marketing partners, Natco Pharma said in a filing to the BSE.

“Natco and its associated marketing partners for the above products in the US, believe that they are the first company to have filed a substantially complete ANDA which includes a paragraph IV certification for Fingolimod capusles and Cabazitaxel injection, providing 180 days of marketing exclusivity upon its final USFDA approval," it added. Novartis sells Fingolimod 0.5mg capsules under the brand name Gilenya in the US market. It is used for the treatment of certain patients with multiple sclerosis.

The market size of Gilenya in the US is around $1.2 billion for twelve months ending September 2014, according to IMS Health sales data.

Sanofi sells Cabazitaxel injection under brand name Jevtana, in the US. The drug is used to treat certain patients with hormone-refractory prostate cancer. As per IMS Health

sales data, the market size of Jevtana in the US was around $116.8 million for the 12 months ended September 2014.

Natco scrip closed at ₹ 1,420.50, up 4.49%, on the BSE.

Topics

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EXHIBIT OO

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/034,340	02/24/2011	Alan H. Auerbach	CGR5001USCNT1

CONFIRMATION NO. 1597

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